REMARKS

This Amendment is responsive to the outstanding Office Action of February 16, 2006, in which claim 245 stands rejected 35 U.S.C. §112, second paragraph, as being indefinite; claims 248, 249, and 252 stand rejected under 35 U.S.C. §112, first paragraph, for failure to comply with the written description requirement; and claims 236, 238, 239, 243-253, and 257-269 stand rejected under 35 U.S.C. §112, first paragraph, for failure to comply with the enablement requirement. Applicant requests favorable reconsideration and withdrawal of the above rejections for reasons set forth below.

Please note that new claims 270-287 have been added to the instant application. Basis for such new claims may be found at pages 45-47, 49, and Examples 18, 19, and 36 of the instant specification.

Applicant submits herewith a Fourth Supplemental Declaration of Dr. Heuser (attached hereto as Exhibit A) and a Third Supplemental Declaration of Dr. Lorincz (attached hereto as Exhibit B). Both of these Declarations render an expert opinion that no more than routine experimentation would be required to practice the invention specified by all of the currently presented claims and that one skilled in the medical art would understand that intravenous and intraluminal administration of growth factors, including cells, is described in the instant patent application.

Prior to discussing the above rejections, Applicant believes that the following remarks relating to procedural and substantive aspects of the prosecution of the instant application are appropriate.

PROCEDURAL ASPECTS

On November 21, 2005, Applicant filed a Request for Continued Examination (hereinafter "RCE") and transmittal Form PTO/SB/(04-05), which specifically instructed the Examiner to enter and consider the following previously filed documents:

1. The arguments and enclosures in the Appeal Brief filed June 9, 2005;
2. The Supplement to Appellant's Brief and enclosures filed August 4, 2005; and
3. The Fifth Supplemental Disclosure Statement (hereinafter "IDS") filed October 21, 2004.

In addition to the above request, Applicant concurrently submitted an Amendment with the RCE.

In response to filing the RCE, the Examiner, at page 2 of the outstanding Office Action, stated that, "Applicant's submission filed on 21 November 2005 has been entered." The scope of such statement was unclear. Accordingly, Applicant's undersigned attorney, Gerald K. White, called the Examiner on March 27, 2006 to request clarification. The Examiner responded to Applicant's attorney, via a voice mail message, on March 30, 2006, which advised that the Appeal Brief had not been considered. The Examiner further advised that it was her impression that the remarks made with the November 21, 2005 Amendment, filed concurrently with the RCE, were intended to be a complete response to the rejections of record. The Examiner also advised, for example, that Applicant did not make specific reference to the Appeal Brief in the Amendment, and, therefore, the outstanding rejection did not refer in detail to the Appeal Brief.

In view of the Examiner's voice mail comments, it is apparent to Applicant that the Examiner failed to comply with Applicant's instruction for the Patent and Trademark Office (hereinafter "PTO") to consider and make of record the arguments and submissions in the Appeal Brief, its Supplement, and the IDS, despite aforesaid detailed instruction. Such failure

obviously extends the length of the prosecution and prevents Applicant and the Examiner from addressing and resolving substantive issues. Applicant again specifically requests and instructs the Examiner to acknowledge that the above-mentioned three documents are made of record.

Rather than engage in further discussion of the above procedural issue or to seek administrative relief by requesting a substitute Office Action, Applicant has incorporated relevant portions of the Appeal Brief and its Supplement into this Amendment to ensure that the presented remarks and associated evidence will be entered into the record and then fully considered by the Examiner. Applicant believes that this course of action will best serve to expedite the prosecution of the instant application by focusing upon substantive matters, rather than procedural, matters. The Examiner's cooperation in fully considering and responding to this Amendment and then framing any remaining issues is requested. The framing and resolution of issues is long overdue, when it is considered that this application has been pending for more than five years.

Setting aside the above discussed procedural aspect, Applicant has carefully considered the rejections of record and the reasoning presented by the Examiner and concluded that the stated bases for the rejections are vague and lack clarity. Specifically, Applicant notes that the Examiner has characterized the bases of the three rejections as "of record." While in the enablement rejection, the Examiner referred to pages 6-20 and 22-26 of the previous Office Action, no such reference was made for either of the other rejections. Merely stating that the current rejection is made for reasons of record fails to provide an adequate basis to permit Applicant to respond to the rejection. The inadequacy of the Examiner's stated basis is further compounded when it is considered that all three of the above rejections, in turn, refer back to prior Office Actions. Such multiple references are improper because the actual basis of the rejection is obscured thereby. The vague nature of the

rejections is further underscored by the fact that claims 238, 239, and 243 were amended, and claims 257-269 were added in the Amendment filed with the RCE. Such claims have not been specifically considered in the present Office Action nor could they have been considered in prior Office Actions. Consequently, Applicant is left to speculate as to how the Examiner intended the prior grounds of rejection to relate to claims 238, 239, 243, and 257-269.

Throughout the course of the instant prosecution, Applicant has attempted to fully respond to all grounds raised by the Examiner, which has resulted in a considerable record. Applicant believes that the Examiner, by not indicating whether or not a prior position is maintained, modified, or withdrawn, has unnecessarily extended the record. For example, the Examiner, by simply stating that the rebuttal has been carefully considered but not found to be persuasive and/or then presenting different reasons to support the rejection, obscures the record and permits many issues to remain unframed. Does the Examiner repeat the first reasons and then complement or replace such initial point? No answer to such question is evident in the record. By merely stating the rejection is maintained for reasons of record, administrative due process has been denied to Applicant.

The outstanding rejection is also believed to be incomplete from the standpoint that Applicant's objective evidence and accompanying arguments have not been fully treated. Many arguments and related evidence throughout the record remain untreated in the Office Action. For example, it is believed that the Examiner has not reached the merits of the various declarations of Drs. Heuser and Lorincz, which are of record. It was error for the Examiner to ignore such declaration evidence. The Examiner must fully consider all evidence presented by Applicant and weigh the evidentiary value thereof *vis-à-vis* any rebuttal evidence that she has provided in order to reach a well reasoned determination of the issues. The instant record lacks such reasoned analysis.

When Applicant's evidence supporting patentability, including that contained in the Appeal Brief and its Supplement, is duly evaluated and given proper weight, it is strongly believed that such evidence far outweighs any rebuttal evidence proffered by the Examiner.

MIXED PROCEDURAL AND SUBSTANTIVE ASPECTS

It is apparent from the length of this paper that the above-mentioned prosecution has resulted in a lengthy record. Firstly, Applicant believes that the major reason for such length is the Examiner's lack of specificity regarding the basis of rejection in each Office Action. The reference to multiple prior Office Actions, coupled with statements that the rejection is for reasons of record, creates an ambiguous record. Secondly, the enablement rejection of all claims on the basis of the term *de novo* necessarily subsumes an earlier rejection regarding intraluminal and intravenous administration. Applicant submits that a better practice would have been to combine these rejections into one rejection and therefore avoid the necessity for repetitive rebuttal. Should the enablement rejection be maintained, the Examiner is requested to combine the respective enablement rejections in a cogent manner, which should serve to reduce the length of any response thereto. Should the Examiner decide to maintain all rejections of record, the Examiner is requested to present a clear, non-ambiguous basis for such rejections, which reiterates and specifically identifies all portions of the record being relied upon. Thirdly, the Examiner's continued refusal to accept the qualifications of Applicant's experts – Drs. Heuser and Lorincz – has also contributed to a burgeoning record. Applicant remains confounded by the Examiner's position. It was the Examiner who suggested that an interventional cardiologist would meet the qualifications of an expert in the field of the claimed invention. Indeed, it is puzzling to Applicant why Dr. Heuser, an admittedly highly qualified interventional cardiologist, does not possess such qualifications.

The Examiner is also requested to follow the mandates of the MPEP and fully treat and rebut all of Applicant's arguments and associated evidence. Such treatment obviously includes identifying and weighing all objective evidence submitted by Applicant *vis-à-vis* that proffered by the Examiner, including Applicant's rebuttal remarks in support of said evidence. Following such requested action would result in defining any remaining issues and serve to place the case in condition suitable for further administrative review. Applicant is requesting that the Examiner literally follow the tenants of compact prosecution and the Final Rejection Practice (Statement of Grounds) outlined in MPEP Section 706.07. Otherwise, Applicant's right of administrative due process will continue to be denied.

SUBSTANTIVE ASPECTS

As will become more evident below, Applicant considers that the Examiner has committed at least two significant substantive errors in the instant prosecution; namely:

(1) The Examiner has read and interpreted the specification to be limited to the specie, cells, despite the generic description and support for the genus, growth factor because the Examiner has ignored the guidance furnished by the Court in Capon v. Eshhar v. Dudas, 76 USPQ 2d 1078, (Fed. Cir. 2005) related to genus-specie description considerations; and

(2) The Examiner has not explored the support for each of the claims, i.e., considered the actual wording and/or limitations of the claims because all claims have been construed to only relate to cells, despite the use of the term growth factor.

Such substantive errors have led to the Examiner's erroneous interpretation and understanding of the disclosed and claimed invention.

Applicant offers the following response to the outstanding Office Action.

Turning to the rejection of claim 245 under 35 U.S.C. §112, second paragraph, as being indefinite, the Examiner states that, "The basis for this rejection is of record" without specifically identifying such "basis."

Presumably, the Examiner is of the opinion that the "multifactorial and non-specific" language recited in said claim is ambiguous because the art allegedly does not use such language to describe cells. Applicant submits that the evidence of record contradicts the Examiner's position. Apparently, the gravamen of the Examiner position is based on the mistaken belief that in order for the questioned language to be definite within the purview of the statute the Applicant must disclose all cells that could possibly meet the limitation of "multifactorial and non-specific."

The Examiner posits that the art's use of the term "multifactorial" is limited to describing, "causes, effects and processes, not cells." As evidence in support of this position, the Examiner refers to "Appendix A" derived from a search of the Medline database. The Examiner refers to six instances where the term "multifactorial" was used in describing diseases, processes or in the context of a study. The Examiner then concludes that each of these usages in the literature support her conclusion that the art does not use the questioned language to describe cells.

Applicant is confounded as to why this ground of the rejection was made and maintained (for reasons that have shifted during the course of this prosecution) because such rejection is not consistent with a prior PTO decision. In the Sixth Supplemental Information Disclosure Statement, Applicant called the Examiner's attention to the fact that parent application Serial Number 08/326,857 was granted to Applicant on June 2, 1998 as Patent Number 5,759,033 (hereinafter referred to as "the '033 patent"). The Examiner failed to respond to such submission, and thus the Examiner's attention is again directed to the '033 patent. Claims 13

and 26 of this patent specify that the claimed growth factor is multifactorial and non-specific. The grant of these claims by the PTO constitutes compelling evidence that the definiteness requirements of 35 U.S.C. §112, second paragraph, were satisfied and that both disputed terms were understood. Applicant submits that the current Examiner's rejection involving such previously accepted terminology is prejudicial to the above-mentioned claims of the patent and has the potential to raise validity issues of the issued patent. Such action amounts to a failure to accord full faith and credit to the previous action of the PTO. See MPEP Section 706.04. Unless the Examiner can provide compelling evidence that the allowance of such claims was erroneous, the earlier action must be maintained. Applicant believes that no such compelling evidence has been presented by the Examiner. To the contrary, Applicant believes that the following remarks and evidence fully demonstrate that the disputed terms are definite and understood by one skilled in the medical art, and thus the prior action of the PTO remains correct and controlling.

Applicant directs the Examiner's attention to the recent *en banc* decision of the CAFC in Phillips v. AWH Corporation, 03-1269-1286, decided July 12, 2005. While the Phillips case involved patent claim infringement, Applicant believes that the principles and authorities expressed in this case are equally applicable for providing guidance to the PTO in determining the meaning of terms in the specification and claims of a pending patent application.

The Phillips decision indicated that the claims of a patent are generally given their ordinary and customary meaning in the art, citing the Vitronics v. Conceptronic, Inc., 90 F. 3d 1582 (Fed. Cir. 1996). Also cited was the Multiform Desiccants, Inc. v. Medzorn, Ltd. Decision, 133 F. 3d 1473, 1477 (Fed. Cir. 1980) for the principle that claims should be read in the context of the patent. The Court in Phillips further observed that extrinsic evidence is less significant than the intrinsic record in determining the legally operative meaning of claim language, citing C.R. Bard, Inc. v.

U.S. Surgical Corp., 388 F. 3d 858, 862 (Fed. Cir. 2000). The Court in Phillips also stated that dictionary evidence can be useful in claim interpretation, but that such evidence is less reliable than the patent specification and its prosecution history. Applicant submits that the Examiner should interpret the words "multifactorial" and "non-specific" in light of the specification as would be apparent to a person skilled in the medical art and thus give such words their ordinary meaning in the art to which the invention pertains. A different interpretation, such as that foisted by the Examiner, bottomed on non-contextual sources, places the term out of context and thus clearly would not be entitled to the same evidentiary weight as the interpretation by a skilled person in the medical art of Applicant's disclosure.

The questioned terms in the specification were "read and understood" by skilled persons in the art, i.e., by Dr. Heuser in his Declaration (of record) and in his concurrently-submitted Fourth Supplemental Declaration and by Dr. Lorincz in his Declaration (of record) and in his concurrently-submitted Third Supplemental Declaration. It is noted that all of the above-mentioned declarations state that relevant portions of the specification regarding multifactorial and non-specific cells were "read and understood" by Drs. Heuser and Lorincz, thereby further underscoring that such terms are understood by those skilled in the medical art.

The Examiner's attempt to support her erroneous position is inapt at best. Applicant likewise conducted a search (using the Google search engine) for the term "multifactorial growth factor" and found references where the questioned term was used to describe growth factors. Applicant identified the J. Biol. Chem., Vol. 280, August 5, 2005 publication (attached hereto as Exhibit C) which relates to using an integrative nuclear fibroblast multifactorial growth factor FGFR 1 and the J. Eukaryot Microbiol., 49(5), 2002, pages 383-390, relating to "Epidermal growth factor (EGF) is a multifactorial growth factor that activates signal transduction events in

mammalian cells..." (attached hereto as Exhibit D). Both fibroblast (FGF) and epidermal (EGF) growth factors are described as multifactorial growth factors on pages 20 and 21 of the instant specification, which are capable of promoting the growth of soft tissue in the body of a patient.

Additionally, the Strauer 2005 reference (of record) clearly describes bone marrow stem cells as multifactorial. The Examiner has apparently admitted this material fact at page 14 of the outstanding Office Action. Further, in 1991, an article authored by Caplan, A.I., entitled "Mesenchymal Stem Cells," Journal of Orthopaedic Research, Vol. 9, No. 5, 1991, pgs. 641-650 (attached hereto as Exhibit E and hereinafter referred to as "Caplan 1991") describes bone marrow stem cells as exhibiting multifactorial characteristics. Applicant believes that Caplan 1991, like the 2001 Caplan et al. post-filing publication designated as Exhibit H in Applicant's Response to the Final Rejection of October 20, 2005, filed December 2, 2005, in co-pending application Serial No. 09/064,000 (attached hereto as Exhibit F and hereinafter referred to as "Caplan 2001"), contains evidence that those skilled in the medical art understand and use the questioned terms in a manner consistent with Applicant's use thereof; and, consequently, there can be no doubt that these terms are definite within the meaning of 35 U.S.C. §112, second paragraph. Caplan 1991 described mesenchymal stem cells ("MSC"), which were harvested from bone marrow and/or periosteum, as comprising multifactorial cells. Specific passages of Caplan 1991 are referenced below in support of Applicant's position.

Regarding Applicant's use of the term "multifactorial cells," which cells are species of the described and claimed genus "growth factor," Caplan 1991 recognized and attributed multifactorial characteristics to MSC at page 641, left column paragraph 1, lines 8-14 and at the top of page summary, lines 6-8.

The first reference at page 641 is as follows:

> Their progeny are affected by a number of factors, however, as they become tracked into very specific developmental pathways in which both intrinsic and extrinsic factors combine to control the molecular and cellular pattern of expression that results in specific tissues that perform specific functions based on their molecular repertoire (9,11).

The second reference at page 641 is as follows:

> Local cuing (extrinsic factors) and the genomic potential (intrinsic factors) interact at each lineage step to control the rate and characteristic phenotype of the cells of the emerging tissue.

As can be appreciated by the Examiner, Caplan 1991 clearly characterizes MSCs as multifactorial cells.

Applicant's search also revealed the Merck Manual of Geriatrics, Ch. 72, Cancer (attached hereto as Exhibit G), which describes "Oprelvekin, a nonspecific growth factor for megakaryocytes" and the NIH Pub Med abstract identifying "Erythropoietin as a nonspecific growth factor and its effect on carcionogenesis" (attached hereto as Exhibit H). Regarding the limitation "nonspecific" cells, species of the genus "growth factor", Caplan 1991 disclosed that MSCs are lineage-nonspecific, i.e., they can develop into nine (9) separate and unique tissues. In this regard, see Fig.1. page 642. Thus, it is patently clear that the art skilled understand the meaning of the term "nonspecific" when applied to cells such as stem cells - they are lineage-nonspecific and can develop into a variety of tissues. For the Examiner to deny this requires a denial of pure science.

It is patently clear that the Examiner's search for "multifactorial and nonspecific growth factor" was incomplete. Clearly, others skilled in the art are comfortable with using the adjectives "multifactorial" and "nonspecific" to describe growth factors, including cells. The Examiner's statement that the specification does not disclose what cells other than stem cells and

germinal cells are multifactorial and non-specific is incorrect. The specification on page 50 further equates multifactorial and non-specific to being pluripotent. Those skilled in the art to which the invention pertains, such as declarants, Drs. Heuser and Lorincz, would understand cells which possess pluripotent characteristics.

In summary, the rejection under 35 U.S.C. §112, second paragraph for indefiniteness should be favorably reconsidered and withdrawn in view of Applicant's body of evidence that the questioned terminology is accepted, understood, and used by those skilled in the medical art. Moreover, the prior Examiner apparently understood and accepted such terminology by granting claims 13 and 26 of the above-mentioned '033 patent. From the weight of evidence presented by Applicant, including the above-mentioned declarations of Drs. Heuser and Lorincz, it appears that the Examiner is the only individual that does not understand the meaning of the questioned "multifactorial and non-specific" used as modifiers for growth factors, including cells. Apparently, the Examiner understood how the questioned language is used as a modifier for "diseases" and "processes" but still does not understand Applicant's use of the same language in connection with growth factors. Such professed lack of understanding of Applicant's usage is inconsistent.

Claims 248, 249, and 252 stand rejected under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." The Examiner, on page 3 of the February 16, 2006 Office Action, states that the "basis for this rejection is of record." The Examiner considered that the language "said injection is intravenous" (claim 248), "said injection is intraluminal" (claim 249), and "angioplasty balloon" (claim 252) has not been described in the subject application in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The gravamen of the Examiner's rejection is the contention that "the instant

specification did not set forth contemplation of a method step wherein cells were administered intravenously, intraluminally, or via angioplasty." Finally, the Examiner, on pages 5 and 6 of said Office Action, states that the rejection is conditioned on the claims reading "on the elected invention, administration of cells, and thus the generic concept of growth factor is not relevant." The administrative and or statutory basis for such a "conditional" rejection is respectfully challenged. However, in any event, Applicant believes that a reasonable reading of the specification by one skilled in the medical art leads to the conclusion that the questioned language is adequately described within the purview of the statute and provides the following explanation.

Initially, Applicant points out that compliance or lack thereof with the "written description" requirement of the statute is a question of fact and must be decided on a case-by-case basis in view of the state of relevant knowledge. Capon v. Eshhar v. Dudas, supra. The initial burden rests with the Examiner to proffer evidence and/or sound reasoning why those skilled in the art, upon reading an applicant's disclosure, would not understand that the applicant was in possession of the claimed invention. See MPEP Section 2163.04 and the authorities cited therein.

The written description requirement does not require an applicant "to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize what he invented and what is claimed." See In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989). All that is required is that, as of the filing date, the disclosure convey with reasonable clarity to those skilled in the art that applicant was in possession of the claimed subject matter. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 1945 USPQ 2d 1111, 1117 (Fed. Cir. 1991). The specification, at page 45, line 1 to page 46,

line 16 contains a statement of Applicant's invention commensurate in scope with the claimed subject matter. Numerous administration species for delivering therapeutic agents to patients, including intravenous, intraluminal, and angioplasty, and numerous growth factors suitable for use in the invention are described. There can be no doubt that the above identified portions of the specification contain an equivalent description of the claimed subject matter, see Eislstein v. Frank, 52 F.3d.1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995). Accordingly, the mere absence of actual working examples in the specification standing alone does not support the Examiner's conclusion that the statutory requirements have not been satisfied.

At page 12 of the November 28, 2003 Office Action, the Examiner concluded that the use of an angioplasty balloon catheter to administer cells was known at the time of the invention; and therefore, it was obvious to use such technique, rather than the technique disclosed by the Murry publication. The Examiner cited Nabel et al. Patent No. 5,328,490 (of record) in this regard. The Examiner's subsequent position that use of an angioplasty balloon catheter is not enabled by the specification (page 45) which describes that "genes (or other genetic material) can be applied with an angioplasty balloon" is at odds with her prior position. Obviously, taking more than one position constitutes inconsistent prosecution.

The significant part of the Examiner's rejection is that Applicant's description on page 45 of the specification of intravenous, intraluminal and angioplasty delivery modes "is limited to use of proteins or nucleic acids (genes or [other, sic] genetic material)" and that there is no suggestion in the specification, "that cells should be administered intravenously or intraluminally." The Examiner states that, "The specification defines 'growth factors' as comprising cells but does not define 'genetic material' as comprising cells." This statement is erroneous because it is clear from the specification that growth factors are included in the genus

"genetic material." In this regard, see page 46, lines 6 and 7 of the specification where it is described that cells and growth factors are types of genetic material. Page 45, in fact, states, at lines 28-29, that "an appropriate gene or other genetic material" may be inserted (emphasis added). The prophetic example, in words, at lines 6 and 7 on page 46 describes that cells, genes, and/or growth factors (or other genetic material) are "placed" adjacent to dead cardiac muscle to grow new muscle and new arteries. Such passage clearly discloses that cells are included under the genus "genetic material." These descriptive words are equivalent to the language recited in the claims. The passages cited by the Examiner as indicating that cells are not genetic material do not, in fact, support such contention. Rather, such passages are consistent with Applicant's use of the term "genetic material" because such passages merely confirm that genes, like cells, are members of the genus "genetic material." The Examiner's conclusion that, "Clearly, this section of the specification is limited to the use of proteins and nucleic acid (genes or genetic material)" is inconsistent with the disclosure at page 45, lines 13-16 because "other genetic material" is contemplated, and genetic material includes cells. Furthermore, the Examiner's conclusion is wrong because starting a continuation sentence with the word "Or" indicates that an alternative (to the preceding sentence) follows and is not meant to exclude. Thus, the continuation sentence beginning with "Or" in the specification at page 45, lines 14-16, indicates that alternative materials (to VEGF materials set forth in the preceding sentence at page 45, lines 13-14) are contemplated. The continuation sentence also indicates that an angioplasty balloon, with the assistance of a vector or any other method, adds alternative administration techniques (to the techniques of the previous sentence, i.e., intravenously, intraluminally, or intramuscularly). For example, all persons recognize that the choice of coffee or tea excludes neither. In the instant situation, one skilled in the medical art would recognize that the choice of

genetic material administered by intravenous techniques, etc. or administered with an angioplasty balloon, etc. excludes neither technique. Likewise, one skilled in the medical art would recognize that the choice of VEGF or genes (or other genetic material) excludes neither. In other words, the two sentences, taken together, from the disclosure at page 45, lines 13-16 indicate that genetic material may be administered by any of the techniques described therein. Thus, the Examiner's contention is erroneous because it overlooks the fact that genes and cells are described as members of the same genus and that the cited passages are consistent with such description.

Viewed in another way, the Examiner's attention is also directed to page 44, lines 19-29 and page 45, lines 19-23 of the specification where it is stated that growth factors (the Examiner, at page 5, lines 13 and 14 of the December 9, 2004 rejection, admitted that growth factors include cells) may be inserted with any of the implant techniques of the invention. The Examiner's admission should serve to conclusively resolve this issue because growth factors include cells, as well as other types of growth factors. The Examiner's requirement that each of these implant techniques must be analyzed in regard to every possible specie of growth factor and reported in the specification does not add descriptive substance. cf. Capon v. Eshhar v. Dudas, supra.

In this regard, the disclosure, at page 45, line 1 to page 46, line 16, includes the claimed administration techniques, as well as a variety of growth factors that lead to the claimed result, i.e., the growth of new cardiac muscle and new arteries. In addition, Applicant's specification, at page 46, lines 3-7 specifically describes seeding with cells and other genetic material to grow new muscle and new arteries. Seeding, of course, is a broad term that is understood by those skilled in the medical art to cover intravenous, intraluminal, angioplasty, as well as other

delivery modes. Thus, there is no question that Applicant broadly disclosed the administration of cells by intravenous, intraluminal, and angioplasty delivery techniques, as well as by other techniques, which constitutes an equivalent description of the claimed subject matter.

The Court in Capon v. Eshhar v. Dudas, supra. in determining that chimeric DNA molecules were adequately described by a generic description observed that the PTO must render sufficiency of disclosure determinations on a case-by-case basis given the state of the prior art at the time of the invention and in view of evidence in the record. The Examiner's attempt to distinguish the present case from Capon by observing that the issue in Capon "was written description of products, not method steps" is inapt. Capon is legal precedent and represents current law in regard to genus–species description issues regardless of whether they involve products or processes. The Examiner must be so guided and follow such precedent in determining whether there is support in the specification for each of the rejected claims.

The Examiner has apparently cited Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ 2d 1961, 1966 (Fed. Cir. 1997) and MPEP Section 2163.02 for the proposition that "the description requirement" requires a showing of an actual reduction to practice in order to establish possession of the claimed invention. Lockwood does not change the standard for showing possession of the claimed invention set forth in In re Gosteli, supra. Rather, Lockwood sets forth a "variety of ways" that possession can be established, such as by using words, structures, figures, diagrams, formulas, etc., to describe the claimed invention with all its limitations. Additionally, Applicant notes that in Lockwood the issue was written description of apparatus (computer system), not methods and involved a 35 U.S.C. §120 benefit issue. Lockwood was denied benefit under Section 120 because of a disclosure hiatus in the chain of applications arising from one of the intervening applications failure to describe a terminal with a

videodisk player. Applicant is understandably confounded by the apparent inconsistency in the manner in which the Examiner applied legal precedent. The Examiner's position in regard to the precedent provided by Lockwood inexplicably diverges from her position in regard to the precedential value of the Capon decision, i.e.; that different statutory classes of invention are involved. The Capon decision represents current law in regard to the description requirement of the statute regarding genus-species issues and its precedential value cannot be summarily dismissed as the Examiner has attempted to do here. Further, the genus-species description issue of Capon is more closely related to the facts of the instant case than the distinct "invention" issue raised in the Lockwood case.

As evident from the above discussion, all of the limitations of the claims at issue appear in the specification in words which describe the claimed transplantation methodology necessary for carrying out the invention. cf Capon v. Eshhar v. Dudas, supra.. Statements in the specification constitute evidence that must be weighed in establishing a *prima facie* case. See In re Margolis, 785 F.2d 1029, 1031, 228 USPQ 940, 942 (CCPA 1986). The Examiner has the initial burden of establishing a *prima facie* case of unpatentability. See In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ 2d 1443, 1445 (Fed. Cir. 1992). Applicant submits that the Examiner has failed to establish a factual basis sufficient to support a *prima facie* case of "lack of description." Simply stated, the Examiner has not articulated wherein the specific disclosure in the specification referred to by Applicant above fails to provide descriptive support for the claimed subject matter. Accordingly, Applicant believes that the Examiner's rejection under 35 U.S.C. §112, first paragraph, for failure to satisfy the written description requirement must fail for lack of a sound factual basis.

From the foregoing discussion, the Examiner's statement that the specification "does not define 'genetic material' as comprising cells" is patently incorrect, and thus it cannot reasonably be concluded that the specification does not convey with reasonable clarity to those skilled in the art that Applicant was in possession of the invention of the subject matter of claims 248, 249, and 252 as of the filing date of the subject application.

Furthermore, Applicant submitted objective evidence in the Second Supplemental Declarations of Drs. Heuser and Lorincz in rebuttal of the Examiner's rejection. These Declarations were submitted with Applicant's Letter dated July 26, 2004, entry of which was noted by the Examiner on page 2 of the Final Rejection of December 9, 2004. The Examiner is again referred to paragraph 10 of each Declaration where Applicant's experts conclude that, "such skilled person would further understand that the disclosures on pages 45 and 46 describe genetic material to include appropriate genes and cells." The Examiner must weigh Applicant's objective evidence proffered in paragraphs 6 and 10 of the Second Supplemental Declarations of Drs. Heuser and Lorincz in meeting the burden of establishing a *prima facie* case of inadequate description. cf. In re Alton, 76 F.3d 1168, 37 USPQ 2d 1578 (Fed. Cir. 1996). Said paragraphs 6 and 10 of these Declarations raise genuine issue of material fact regarding what the specification disclosed to one skilled in the art. The Second Supplemental Declarations of Drs. Heuser and Lorincz confirm that one skilled in the art would understand that Applicant's specification described genetic material to include cells; and, therefore, the burden of going forward with evidence to the contrary shifted to the Examiner to show that one skilled in the art would not so understand the specification.

In the Final Rejection of December 9, 2004, regarding the written description requirement, the Examiner apparently ignored the conclusions reached by Drs. Heuser and

Lorincz in their above-mentioned Second Supplemental Declarations; namely, that cells are included in the description of the invention. These expert declarants placed Applicant's invention in the context of the state of relevant knowledge in the art and expounded upon how the identified portions of the specification would be understood by persons of skill in the field of the invention. Further, the Examiner is referred to the new Declarations submitted with this Amendment. The Examiner should have considered paragraphs 6 and 10 in said Second Supplemental Declarations because such Declarations contain evidence that these two skilled physicians understand that cells are described by the term "genetic material" and further that cells are understood to be described as materials which may be implanted in accordance with the delivery modes mentioned at page 45, lines 13-16 of the specification. It is incumbent upon the Examiner to articulate how the Declarations failed to overcome the initial case for rejecting the claims in issue. In re Oetiker, supra. Therefore, the Examiner failed to weigh all the evidence in the record and, perforce, erred as a matter of law. cf. In re Alton, supra.

Moreover, it is well known in the medical art that cells contain genetic material. In this regard, see the entry "Cell (biology)" from Wikipedia, the free encyclopedia, on page 3 under the major heading "Genetic material" (attached hereto as Exhibit I) and the University of Texas Medical Branch, Cell Biology Graduate Program publication entitled, "The Cell Nucleus" (attached hereto as Exhibit J). These two publications are cited to confirm the specification's disclosure that cells are genetic material.

To place the written description rejection in proper perspective in the instant case, it is noted that the rejected claims are those elected following a species restriction requirement by the Examiner between genes and cells. Although Applicant elected to prosecute claims directed to cells, the specification is not so limited. It is clear that Applicant's specification discloses, for

example, the genus genetic material, the subgenus cells, and the species stem cells including bone marrow stem cells, and thus fully provides descriptive support for the invention in the instant application. It is also clear that the specification includes genes as a subgenus under the genus genetic material. The specification was written to utilize generic terms and expressions to convey information regarding all subgenuses and species. Applicant believes that the Examiner failed to take such perspective into account when making this rejection and thus erroneously required that a strict antecedent basis for all species and administration techniques be set forth in an exemplary manner whenever a generic term is used in the specification. At pages 5 and 6 of the Final Rejection of December 9, 2004, the Examiner pointed to various passages in the specification that purported to show that portions of the specification were limited to genes or genetic material. Such conclusion is erroneous for at least two reasons. First, as demonstrated above, the term genetic material includes cells. Second, a gene is a subgenus of genetic material. Therefore, such passages merely confirm to one skilled in the art that Applicant contemplates such materials. The cited passages are consistent with Applicant's use of broad terminology and merely discuss or exemplify one subgenus or specie that may be used in accordance with such passage. Certainly, such passages are not inconsistent with the terminology. Applicant's disclosure, coupled with the evidence proffered by the Supplemental and the Fourth Supplemental Declarations of Dr. Heuser and the Supplemental and the Third Supplemental Declarations of Dr. Lorincz, far outweighs any *prima facie* case for rejecting claims 248, 249, and 252 for lack of description, which may have been articulated by the Examiner.

Finally, Applicant observes that the rejection appears to be based upon a hypertechnical application of 35 U.S.C. §112, first paragraph, description requirement, should be withdrawn in view of the interpretation given this statutory requirement in a line of decisions exemplified by

In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA, 1970); In re Borkowsky, 422 F.2d 904, 164 USPQ 642 (CCPA, 1970); and In re Wakefield, 422 F.2d 897, 164 USPQ 636 (CCPA, 1970) and Capon v. Eshhar v. Dudas, supra.

Claims 236, 238, 239, 243-253, and 257-269 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner concludes that the rejected claims call for "subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner further states that, "The basis for the rejection is of record. See pp. 6-20 and 22-26 of the previous Office Action (mailed 09 December 2004)." Such pages refer back to the prior rejection of November 28, 2004.

Claims 248 and 249 were finally rejected under 35 U.S.C. §112, first paragraph, "as failing to comply with the enablement requirement" (pages 6-20 of the Final Rejection of December 9, 2004). Such Office Action further referred back to the rejection applied in the Office Action of November 30, 2003 which stated that, "The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Although the Examiner's above-mentioned statements of the rejection failed to set forth any specific or cogent grounds for the rejection, Applicant's understanding is that the rejection is based on a lack of enablement for the administration of a growth factor by intravenous and intraluminal techniques to a patient's heart to achieve the growth of new cardiac muscles and new arteries because claims 248 and 249 specify such techniques. The Examiner has improperly attempted to interpret such claims as being limited to cells as the growth factor. However, no such limitation appears in the claimed invention and the claims must be interpreted in light of

actual content, not by the Examiner's desired content. Applicant respectfully disagrees that the invention defined in the claims fails to comply with the enablement requirement of the statute.

It is apparent, based upon the Examiner's remarks in the Final Rejection of December 9, 2004, that the Examiner considered that claims 248 and 249 are directed to a method for the repair of dead/damaged portions of a human heart. However, such remarks are erroneous because these claims require only growth of new cardiac muscle and a new artery. In view of such erroneous reading of the subject matter of the claims, the rejection of claims 248 and 249 should be reconsidered and examined in light of the actual claimed subject matter. For the sake of completeness, Applicant has addressed all issues raised by the Examiner, whether or not they are directed to the claimed subject matter.

Prior to discussing the above rejection in detail and addressing the prior points raised by the Examiner (as best understood by Applicant), Applicant believes that it is important for the Examiner to focus upon several factors underlying the rejection so that the rejection and disclosed and claimed invention can be placed in proper perspective.

Following a ninety-four-way restriction requirement, Applicant elected to prosecute the claims of the Group 79 invention. The claims for such invention were specified by the Examiner to be claims 204 and 205. Applicant subsequently added claims 236-253 on July 1, 2003 as readable upon the elected invention. The Examiner then made a further restriction requirement on August 25, 2003 to which Applicant elected the Group III invention designated by the Examiner as claims 204, 205, 236-239, and 243-253. Such claims form the basis for the claims under prosecution. Inasmuch as the Examiner grouped and identified such claims as the elected invention, it is the Examiner's responsibility to fully, not partially, treat the actual subject matter of such claims.

Another point to consider is that Applicant made and disclosed a generic invention wherein growth factors, including genes and cells, were applied with a variety of disclosed administration techniques to achieve the novel and unobvious results of the invention. The Examiner must fully consider and give weight to such generic disclosure when evaluating enablement.

Applicant also wishes to address an important issue underlying the instant prosecution, i.e. consistency of examination standards applied by the PTO. The PTO is obligated to apply uniform standards of examination to maintain prosecution integrity and thereby ensure that administrative due process is accorded to all applicants.

Applicant believes the Examiner has applied inconsistent standards in her concurrent examinations of the instant application and *vis-à-vis* U.S. Patent No. 6,844,312, issued on January 18, 2005 to Weiss et al. (attached hereto as Exhibit K and hereinafter referred to as "the Weiss patent"). This patent generally relates to and contains broad claims to the use of stem cells to treat Parkinson's and other diseases.

The Weiss patent, like the present invention, claims treating a patient with stem cells to achieve a new result, i.e., Weiss ameliorates Parkinson's disease by growing "new" neurons, and Applicant grows new cardiac muscle, a new artery, and may repair a dead or damaged portion of a heart. The file history of the Weiss patent reveals that the Examiner, unlike in the prosecution of the instant application, never challenged the enablement of the disclosed invention regarding the preparation or handling of stem cells, the enablement of intravenous and intraluminal stem cell administration techniques, and stem cell dosages or cell concentrations. The Examiner's sole challenge was to the scope of Weiss' novel therapeutic mixture. In contradistinction, in the prosecution of the present invention, the Examiner concluded that enablement was not present

based in part upon the above enumerated stem cell factors. The inconsistency between the respective prosecutions is especially egregious in view of the fact that the present invention claims the use of old materials and old techniques – not the use of new compositions. Moreover, unlike in the Weiss prosecution, Applicant has proffered objective declaration evidence, which raises genuine issues of material fact regarding what the instant application disclosed to enable one skilled in the medical art to make and use the claimed invention, thereby further highlighting the inconsistency between the respective prosecutions.

It is important to note that the first paragraph of the statue requires nothing more than objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. As a general matter, an application disclosure, which contains a teaching of how to make, and use the invention in terms which correspond in scope to those used in describing the invention sought to be patented is considered to be in compliance with the enabling requirement of the statue. In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367, 369-370 (1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." [Emphasis added]. In re Robins, supra.

The questioned intravenous and intraluminal administration techniques were well established in the medical art prior to Applicant's invention. That cells, including stem cells, were well known and characterized prior to Applicant's claimed invention is also an established fact. Another established fact is that stem cell banks were created as early as the 1950's indicates that those skilled in the medical art were familiar with harvesting, handling, culturing, preserving, separating, and storing, etc. such stem cells. Caplan 1991 reported culturing human bone marrow and isolating mesenchymal stem cells. Dr. Elia's contribution to the medical art as

it pertains to the claims, however, was that growth of new cardiac muscle and a new artery, as well as heart repair, could be accomplished through use of a new combination of old administration techniques and old growth factors, including cellular materials. Knowledge of the above facts compels the conclusion that one skilled in the medical art could read Applicant's disclosure of the invention and the claims in issue and reasonably determine that such disclosure would enable one skilled in the art to make and use the claimed invention without recourse to more than routine experimentation. Certainly, the expert opinions of Drs. Heuser and Lorincz confirm this conclusion.

The evidence relied upon by the Examiner in reaching the conclusion of lack of enablement appears to consist essentially of the Strauer et al. (hereinafter "Strauer") publication cited by Applicant as Exhibit I in the Amendment filed February 17, 2004, and the Deb et al. (hereinafter "Deb") publication cited by Applicant as Exhibit II in the Amendment filed February 17, 2004. Both publications bear a date later than Applicant's filing date.

The Examiner relied on Strauer as evidence of non-enablement of the claims reciting intravenous administration of cells. At the bottom of page 7 of the Final Rejection of December 9, 2004, the Examiner concluded that Strauer is "not particularly relevant" to the rejected claims because such claims are directed to intravenous and intraluminal administration techniques. Applicant points out that Strauer's technique and intravenous administration are both types of intraluminal administration.

Strauer was described by the Examiner at page 12 of the Final Rejection of December 9, 2004, to utilize "a specialized form of intraluminal delivery, specifically, balloon catheter injection" where high-pressure injection was utilized while the angioplasty balloon was inflated to avoid a "wash-away" effect of standard intraluminal injection. The word "specialized"

appears to be that of the Examiner, as it is not used by Strauer to characterize his process. In any event, whether or not the technique of Strauer may be characterized as "specialized," it is evident that many other techniques may be used to perform the claimed method; thus, disclosing the specific technique of Strauer is not required to constitute enablement of Applicant's invention. In this regard, Wollert et al. (hereinafter "Wollert") cited as Reference AP in Applicant's Third Information Disclosure Statement, mailed July 27, 2004, utilized a procedure essentially the same as that disclosed by Strauer, except that Wollert utilized a conventional, off-the-shelf angioplasty balloon to infuse cells without describing any need for high pressure. Applicant cited Wollert as evidence that high-pressure injection of cells, such as reported by Strauer, is not required to achieve heart repair and that providing a sufficient number of cells and preventing remigration are not insurmountable problems, as alleged by the Examiner. It was error for the Examiner not to consider the evidence contained in Wollert. The Wollert publication verifies this fact, and the Examiner has provided no rebuttal thereof other than to allege that, even though not disclosed, Wollert must have used high pressure. Accordingly, Applicant's failure to mention high pressure in the specification is of no moment because Wollert demonstrates that successful implantation does not require high-pressure infusion.

Strauer did not state that other administration techniques, such as intramuscular or intravenous, were inoperative but instead considered such techniques not as effective and concluded that "intracoronary administration obviously seems to be advantageous..." (Page 1917, left column, lines 26 and 27). A fair reading of the text at page 1917, first and second full paragraphs of the left column, indicates that Strauer did not consider intravenous administration to be inoperative, as erroneously alleged by the Examiner, but was simply not preferred on the basis that multiple passages could be required.

As mentioned above, the Examiner relied upon a portion of Strauer where alleged "shortcomings" of intravenous and intraventricular administrations are discussed. Both types of administration are species of intraluminal administration. Such portion may be found in the first full paragraph in the left column on page 1917 as set forth below:

> The second question was how to deliver the cells most efficiently. When given intravenously, only a very small fraction of infused cells can reach the infarct region after the following injection: assuming a normal coronary blood flow of 80 mL/min per 100 g of LV weight, a quantity of 160 mL per left ventricle (assuming a regular LV mass of ~200 g) will flow per minute. [31, 32] This corresponds to only about 3% of cardiac output (assuming a cardiac output of 5000 mL/min).[34] Therefore, intravenous application would require many circulation passages to enable infused cells to come into contact with the infarct-related artery. Throughout this long circulation and recirculation time, homing of cells to other organs could considerably reduce the numbers of cells dedicated to cell repair in the infracted zone. Thus, supplying the entire complement of cells by intracoronary administration obviously seems to be advantageous for the tissue repair of infracted heart muscle and may also be superior to intraventricular injection[33] because all cells are able to flow through the infarcted and peri-infarcted tissue during the immediate first passage. Accordingly, by this intracoronary procedure the infarct tissue and the peri-infarct zone can be enriched with maximum available amount of cells at all times.

Clearly, from the above quote, Strauer does not indicate that intravenous and/or intraventricular administrations are inoperative but only that such techniques are less efficient than Strauer's high-pressure intraluminal technique. By stating that his technique, "seems to be advantageous...and may also be superior" to other forms of injection, Strauer does not raise a genuine issue of material fact and clearly does not establish inoperability of other forms of administration, as alleged by the Examiner. Thus, the Examiner's reading of Strauer is misleading and inaccurate. To the contrary, such statement would merely inform one skilled in

the medical art that intravenous administration may not be as efficient as the technique used by Strauer. Certainly, Strauer never states that intravenous administration of cells would be inoperative; in fact, Strauer 2003 (of record) in the section captioned, Route of Cell Administration, states that, "The intravenous route of administration is easiest." Note further that intravenous administration is illustrated in the figure in such section. Based upon the above-mentioned disclosure, no skilled person in the medical arts would agree with the Examiner's conclusion, "Thus, Strauer specifically provides evidence of non-enablement of the instant claims reciting intravenous administration of cells." Clearly, the Examiner has misinterpreted and misunderstood Strauer. The Examiner's attention is also directed to the fact that other types of administration techniques are referred to as "preferred" in Strauer 2003. Obviously, a preference does not mean that other types of administration are not enabled. Lest there be any doubt that intraveneous implantation would constitute a viable administration route, such doubt should be removed by reviewing a recent article entitled, "Osiris Reaches Safety Milestone in Stem Cell Clinical Trial for Cardiac Patients" published by Osiris Therapeutics, Inc. (attached hereto as Exhibit L) announcing the U.S. Food and Drug Administration's (FDA's) approval of a Phase I Clinical Trial for intraveneous administration of stem cells. Of particular importance is Osiris' reported use of a "standard IV line" with the expectation that implanted stem cells will migrate to the injured area of a heart as a result of the "body's own signals." It appears that the Osiris clinical trials follow Dr. Elia's disclosed IV heart repair technique. With the FDA's approval of such trials and the other evidence of record, there can be little question of the enablement of intraveneous administration.

Moreover, there is no evidence that Strauer, in fact, conducted any side-by-side experimentation with any other delivery modes to support such consideration, and thus such

statement is speculative. The Examiner failed to appreciate that to have an enabling disclosure, an applicant is not required to foresee, invent, and disclose future improvements to standard, known techniques. Under current law, an applicant is not required to foresee, invent, and disclose improvements and enhancements to the basic invention to provide an enabling disclosure. Merely because Strauer reported that his high-pressure push technique provides good results does not mean that Applicant's specification does not provide an enabling disclosure as of the filing date of the subject application. cf. Hormone Research Foundation v. Genetech, Inc., 904 F.2d 1558, 15 USPQ 2d 1039 (Fed.Cir.1990). All an applicant is required to do is provide a disclosure that one skilled in the art can understand and then follow to make and use the invention. Thus, any failure to disclose a later developed technique has no bearing upon enablement.

The Examiner's above analysis overlooks the commonly known fact that both intravenous and intraluminal administration are well established in the medical art as techniques for introducing various substances into the body of a patient. Intravenous administration, in particular, is routinely used for such introduction. Inserting a substance into a vein of a patient, where it mixes with blood and is transported throughout the body by the circulatory system, results in treatment of a desired area. Inasmuch as all blood circulates through the heart, the heart itself is a prime candidate to be treated by intravenous administration.

It is also pointed out that in the prosecution of the Weiss patent, the Examiner, unlike in the instant application, made no enablement challenge to the broadly disclosed and claimed administration techniques, including intravascular and intramuscular, even though the treated site was the brain – a site more remote than the heart. See column 8, lines 25-37 of the Weiss patent in this regard.

In the challenge to the qualifications of Drs. Heuser and Lorincz at page 7 of the Final Rejection of December 9, 2004, the Examiner raised generalized concerns regarding the properties and handling of cells. Such concern by the Examiner amounts to an expression of opinion rather than factual evidence. The properties of cellular materials were well established and well known in the medical art prior to Applicant's filing date. Official Notice can be taken that stem cell isolation and culture techniques have been known and used decades prior to Applicant's filing date. In any event, Applicant calls the Examiner's attention to four publications. Exhibits F, G, and H of Appellant's Brief (of record) confirm the above-mentioned facts and which are believed to fully resolve any issue created by the Examiner's concerns. While such exhibits speak for themselves, Applicant makes the following comments regarding prior Exhibit III (cited in Applicant's Response to Final Rejection). Exhibit III is an article published in 2002 by Pediatric Transplantation entitled, "Milestones in the Development of Pediatric Hematopoietic Stem Cell Transplantation – 50 Years of Progress." This publication is a review article summarizing fifty years of practice, and thus supports the fact that stem cell handling and preparation techniques have been known for decades. Exhibit III illustrates that cell handling and isolation techniques were well known for separating MSC's. Above-mentioned Exhibits F, G, and H further demonstrate that stem cell isolation and culture techniques have been known and used decades prior to Applicant's filing date and constitute probative evidence that fully rebuts the Examiner's unsupported "concerns."

The Examiner's challenge to the qualifications of Drs. Heuser and Lorincz also opined that stem cells are not like other drugs routinely administered in the art. Applicant respectfully disagrees with such unsupported opinion because bone marrow stem cell harvesting and administration are well-established protocols. The Examiner also opined that, "they [cells] have

to be handled delicately so as to avoid mechanical or chemical rupture of the cell membranes." The factual evidence that Strauer utilized "high-pressure injection," which functioned for the intended purpose and apparently did not result in mechanical or chemical rupture of the cell membrane, negates this opinion. There is no evidence to support the Examiner's opinion, and the evidence contained in Strauer clearly rebuts such opinion.

From the above discussion, it is evident that the Examiner has raised unfounded "concerns" regarding cell handling and preparation and has failed to provide any evidence supporting the validity of such concerns. These concerns are based upon the Examiner's unsupported opinion and speculation and are not entitled to evidentiary weight. On the other hand, Applicant has provided objective evidence rebutting the Examiner's unsupported opinion, which indicates that the Examiner's concerns are speculative and have already been addressed and resolved in the medical art for years prior to Applicant's filing date. Thus, the Examiner's speculative concerns are unfounded and are not supported by any evidence of record, whether used to challenge the qualifications of Drs. Heuser and Lorincz or to challenge the enablement of claims 248 and 249.

At pages 14 and 15 of the Final Rejection of December 9, 2004, regarding the enablement of claims 248 and 249, the Examiner admits that Deb "provides evidence that bone marrow cells, administered intravenously, can migrate to the heart." Such admission should end any speculation, and indeed confirm, the operability of intravenous administration of cells as disclosed in Applicant's specification. Inasmuch as intravenous administration is a specie of intraluminal administration, Applicant believes that the Examiner's admission pertains to both types of administration.

The Examiner also alleged that Applicant cited Deb for the proposition that, "human

bone marrow can be used as a source of extracardiac progenitor cells capable of de novo cardiomyocyte formation." Such allegation is erroneous because it was Deb, (at page 2 in the Conclusions section) rather than Applicant, that made such statement. Instead, Applicant cited Deb to rebut the Examiner's erroneous contention that intravenously injected cells would not migrate to the heart. Clearly, Deb verified such migration, and the Examiner has so admitted.

Moreover, the Examiner stated at page 15 of the Final Rejection of December 9, 2004, "The Deb et al. publication is the only evidence that addresses administration of cells at a site other than exactly at the infarct zone." Such statement is clearly erroneous. Strauer administers an intracoronary (intraluminal) injection near the infarcted zone. On page 1914 in Figure 1, Strauer clearly states the "catheter enters the infarct-related artery and is placed above the border zone of the infarction." Thus, Strauer confirms that intraluminal administration of cells is an operative administration technique. The cells must migrate in order to physically get outside of the infarct-related vasculature and into the dead heart muscle. As a result of said migration, "The cells are therefore able to reach both the border and the infarcted zone" of the heart. Wollert produced similar results to those of Strauer, with the exception that Wollert delivered autologous bone marrow cells (BMC's) via the central lumen of an off-the-shelf balloon catheter without the need for pressure infusion. Thus, Strauer, Deb, and Wollert all provide evidence that migration to the heart occurs with intravenous and intraluminal administrations of cells. Such evidence should serve to fully resolve this issue.

The Examiner has criticized Deb for not providing sufficient dosages to effect heart repair. Such criticism is misplaced because claims 248 and 249 do not require heart repair, and Deb did not attempt heart repair as erroneously implied by the Examiner. Deb reported human autopsy evidence of cardiomyocyte formation, which validates the claimed invention. All of the

patients in the Deb study received routine bone marrow transplantation dosages, which had been well-established protocol for decades. Certainly, the amount of cells administered by Deb was sufficient to grow new cardiac muscle because Deb reported such growth. In any event, Deb, in the table on page 1248, makes it clear that the patients all had some form of leukemia; and at lines 14 and 15 of the same page states that, "no patients in our study group had histological evidence of myocardial inflammation." Thus, it is of no moment whether or not the amount of cells injected by Deb was sufficient to cause heart repair because, as stated by Deb, the study was not directed to patients undergoing treatment for repairing a dead or damaged portion of a heart. Strauer speaks of remigration and theorizes that intravenous application would possibly require many circulation passages to enable sufficient cells to come into contact with the heart. Further, Strauer merely states, at page 1917, first column, lines 42-46 that, "[p]resumably, ..., fewer cells were lost ... " due to remigration when delivering the cells by intracoronary administration. The Examiner has not identified any teaching in Strauer that intravenous administration techniques would be inoperative. Moreover, multiple (sequential) administration of cellular materials is common in the medical art, as evidenced by Strauer, who contemplated using up to seven infusions for his intracoronary technique. Thus, one skilled in the art utilizing an intravenous administration would understand that multiple dosages could be utilized for achieving new cardiac muscle growth, new artery growth, and heart repair, as illustrated by Strauer. The specification at page 45, lines 26 and 27, discloses that it may be necessary to sequentially administer the growth factor. It is a notoriously well-known and common practice in the medical art to administer multiple dosages of substances, such as cells, intravenously.

The Examiner's attempt, at pages 14 and 15 of the Final Rejection of December 9, 2004, to couple the teaching of Deb with the disparate teaching of Strauer to establish that the use of

"intravenous administration of cells to repair a dead or damaged portion of a heart has not been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and preventing them re-migrating away from the site" is inapt. In fact, a fair, reasoned reading of Strauer and others in the field indicates otherwise. Applicant points out again that claims 248 and 249 do not require heart repair, and thus the Examiner's statement is irrelevant to the claimed subject matter. In any event, the Examiner has pointed to no evidentiary basis in this record to support such a conclusion.

As stated above, coupling Deb and Strauer is obviously inappropriate because Deb, unlike Strauer, is not attempting to repair a heart. A more reasonable reading and understanding of the respective, independent teachings of Strauer and Deb leads to the conclusion that intravenous administration of cells would result in the growth of new cardiac muscle and new arteries. A fair reading of Strauer clearly indicates that intravenous administration would be operative and likely could involve multiple passages. Again, see Strauer at page 1917 and Strauer 2003, in this regard. A fair reading of Deb indicates that intravenously administered stem cells travel to the heart and produce cardiomyocytes. Thus, once Applicant's inventive concept was understood, it would be well within the skill of the art to select an appropriate number of cells (dosage) and number of infusions to achieve the desired result for reasons fully addressed later by Applicant.

Providing a sufficient number of cells and preventing "remigration" are not shown by the Examiner, in fact, to be insurmountable problems because, as pointed out earlier, Wollert is operative to repair a human heart. Applicant again points out that claims 248 and 249 are not directed to heart repair. In any event, because repair occurred, Wollert clearly must have provided a sufficient number of cells and overcome problems, if any, associated with

"remigration." Rather, such alleged problems concern efficiency, not operability, and do not constitute "evidence of nonenablement" as alleged by the Examiner. As will be noted below, Drs. Heuser and Lorincz disagree with the Examiner's conclusion. Once again, the Examiner has fabricated problems that extend beyond the disclosure and claims rather than addressing such expert opinions. It is well established that an invention does not need to work in an optimum manner to meet the requirements of the patent statutes.

In summary, Applicant believes that the Examiner's evidence of lack of enablement, which comprises the Examiner's erroneous assessment of Strauer and Deb, as discussed above, when considered *vis-à-vis* the evidence of enablement provided by Applicant's specification combined with a fair and reasonable reading of Strauer and Deb, coupled with Wollert, fails to establish a *prima facie* case of lack of enablement under current law. Thus, this rejection should be reversed.

Assuming, *arguendo,* that a *prima facie* case was somehow established by the Examiner, the record contains additional objective evidence in the form of declarations proffered by Applicant that is ample to rebut any such case. During an interview on May 22, 2003, the Examiner stated that an expert opinion from an interventional cardiologist would be helpful in regard to establishing the operability of the claimed methods. Based upon such statement, Applicant identified Dr. Richard Heuser. Applicant also identified Dr. Andrew Lorincz because he is highly skilled in genetics, a field of medicine also clearly related to the claimed invention. Applicant submitted initial Declarations of Drs. Heuser and Lorincz as evidence of what the application disclosed to one skilled in the art. Applicant subsequently proffered two Supplemental Declarations of Drs. Heuser and Lorincz. In addition, a Third Supplemental Declaration of Dr. Heuser (attached hereto as Exhibit M) is enclosed to respond to the criticisms

raised by the Examiner in the Final Rejection of December 9, 2004. The Third Supplemental Declaration of Dr. Heuser was previously submitted with Applicant's Appeal Brief. A second copy of such Declaration is enclosed herein for the Examiner's convenience.

In addition to the above-mentioned Declarations, Applicant concurrently submitted a Fourth Supplemental Declaration of Dr. Heuser and a Third Supplemental Declaration of Dr. Lorincz. Both of these Declarations render an expert opinion that no more than routine experimentation would be required to practice the invention, as specified by all of the current claims.

In the Final Rejection of December 9, 2004, at page 7, the Examiner apparently determined that the original and two Supplemental Declarations under 37 CFR 1.132 of Drs. Heuser and Lorincz were insufficient to overcome the initial enablement rejection. The Examiner specifically challenged these Declarations on two grounds; namely, 1) "while it is clear that Drs. Heuser and Lorincz are accomplished physicians, it is noted that none of the Declarations...or the Supplemental Declarations...report experience with cellular therapy as required by the instant claims." (page 7); and 2) "are based upon evidence that is found to be either irrelevant, not commensurate in scope with the claims, or relying upon methods which were not disclosed in the specification as originally filed" (page 10). It is noted again that not all of the claims under examination require the administration of cells, as certain of the claims, including claims 248 and 249, are drawn to the genus growth factor. Regarding the first ground, as will be demonstrated below, Drs. Heuser and Lorincz are eminently qualified to render their respective opinions. Regarding the second ground, these opinions are based upon Applicant's specification and are not, as erroneously alleged by the Examiner, based upon any other extraneous evidence.

On July 26, 2004, Applicant submitted Second Supplemental Declarations of Drs. Heuser and Lorincz, which contained additional information regarding their respective qualifications to render their expert opinions. Dr. Heuser provided additional background information affirming his knowledge of "cell therapy." Dr. Lorincz provided information indicating his familiarity with stem cell technology, including bone marrow preparation. The Examiner, at page 10 of the Final Rejection of December 9, 2004, further challenged their respective qualifications by raising new issues. Applicant, in an attempt to answer such newly raised issues, submitted a Third Supplemental Declaration of Dr. Heuser directed to the new issues raised by the Examiner. Paragraph 5 of the attached Third Supplemental Declaration provides clarification that the device described in Dr. Heuser's U.S. Patent No. 6,190,379 has been utilized to administer protein and/or muscle cells to the myocardium. Dr. Heuser also provides further detail regarding his role in Bioheart, Inc.'s trials involving the administration of cells to the heart. Applicant considers that such additional information fully responds to the Examiner's newly raised concerns and believes that all issues of qualification are satisfied, particularly because the Examiner has not cited any evidence that recognizes "cellular therapy" as a medical specialty and, as a consequence, any qualifications pertaining to "cellular therapy" are unknown and undefined. The Examiner has failed to respond to this issue.

It is apparent that the clinical investigation team conducting the Strauer experiments comprised cardiologists and other highly skilled medical professionals, and that the Examiner has not specifically pointed out where the Strauer team possessed expertise different from Drs. Heuser and Lorincz. Applicant notes that the investigative team of the Murry publication was apparently led by Charles E. Murry, M.D., Ph.D., Dept. of Pathology, University of Washington. Clearly, the Strauer and Murry teams do not appear to exhibit an expertise in heart repair that

significantly differs from that of Drs. Heuser and Lorincz. Rather, it is clear from the record that what skilled workers in the art of regenerative medicine in the cardiac field such as Wollert, Strauer and Perin have in common with Dr. Heuser is that they are all qualified cardiologists.

Regarding the claimed intraluminal and intravenous administration techniques, Applicant notes that Dr. Heuser's CV indicates extensive experience in the administration of various materials, including growth factors, to the heart. For example, Dr. Heuser's CV is replete with medical journal articles, book chapters, and books dealing with intraluminal placement of various appliances and devices, including those described by Strauer. The PTO is requested to take Official Notice that physicians, such as Drs. Heuser and Lorincz, are quite familiar with the well-known administration techniques of intravenous and intraluminal injection. Individuals having far less qualifications than physicians routinely perform cellular intravenous injections, such as blood/bone marrow transfusions.

Regarding cells and administration techniques, Dr. Heuser's Second Supplemental Declaration states that he was granted U.S. Patent No. 6,190,379 for a hot tip catheter. The Third Supplemental Declaration, at page 5, states that this catheter has been used for the delivery of protein and/or muscle cells to the myocardium. The Examiner indicated that the word "cell" does not appear in the patent. Applicant agrees with the Examiner that such word does not appear in the patent but points out that Dr. Heuser's Third Supplemental Declaration refers to the use of the device covered by the patent, not the disclosure of the patent.

The Examiner, at page 10 of the Final Rejection of December 9, 2004, alleged that there was no evidence to support Dr. Heuser's statement that he had worked in gene therapy. Such allegation is erroneous because it ignores the fact that a declarant's sworn statements constitute evidence, in and of themselves.

Dr. Heuser is a member of the Scientific Advisory Board of Bioheart, Inc., a world leader in cellular muscle repair of the myocardium. Dr. Heuser's Third Supplemental Declaration provides further detail as to his advisory role in the performance of trials involving cellular administration to the heart. Clearly, he is an expert in the field of medicine pertaining to the invention and would be recognized by his peers as eminently qualified to review the disclosure and claims and to render the expert opinions based thereon.

Applicant identified Dr. Lorincz as an expert because he is skilled in genetics – a field of medicine related to the claimed invention. Considering Dr. Lorincz's educational and professional experience, it is evident that he is also qualified to render an expert opinion regarding Applicant's enablement of the claimed invention.

Dr. Lorincz stated in his Second Supplemental Declaration that he is familiar with stem cell technology, including bone marrow preparation. Such familiarity, coupled with other work involving cellular products previously outlined in his CV, leads to the conclusion that a reasonable person being familiar with the medical art would recognize that Dr. Lorincz is highly qualified to render an expert opinion in the instant patent application. The Examiner's attention is directed to "Fluorescent Microscopy of DES-induced Morphologic Transformation in Unfixed, Cultured Cells" which appeared in Journal of Oral Pathology and Medicine and is located in the Bibliography section of Dr. Lorincz's CV. The Examiner's attention is also directed to "Biochemical Genetic Defects" published in the Journal of The Florida Medical Association and located in the Editorials and Commentaries section of Dr. Lorincz's CV. Moreover, Dr. Lorincz personally informed Applicant's representative, Dr. Jerry W. Bains, of an unreported study involving Dr. Lorincz's assessment of stem cell infusions into patients to correct Hurler's Syndrome by transplanting cord blood stem cells. Dr. Lorincz's CV is replete

with references to Hurler's Syndrome as well as other cellular studies. Dr. Lorincz is currently Chairman of Vitalflor, a company involved in the observation of cells in the microscopy assessment of vitally stained living cells and living organisms. Dr. Lorincz was granted the following three U.S. patents: No. 5,812,312 (incorrectly identified as Patent No. 5,812,314 heretofore in the record) entitled Microscope Slide; No. 6,239,906B1 entitled Flexible Microscope Slide; and No. 6,567,214B2 entitled Microscope Slide Having Culture Media and Method for Use. These patents relate to special stains useful in such assessments.

Applicant believes that the fact that the Declarants have diverse backgrounds and that each rendered an opinion stating that the specification enables one skilled in the art to make and use the claimed invention constitutes compelling, probative evidence. Applicant's belief is reinforced by the fact that Strauer's investigational team members had expertise in diverse fields. Accordingly, the above-mentioned qualifications of Dr. Heuser and Dr. Lorincz, in combination with the Examiner's admissions in the Final Rejection of December 9, 2004, at page 10, lines 19 and 20 that, "Again, it is clear that Dr. Heuser is an eminent, highly accomplished cardiologist," and at page 11, lines 20 and 21 that, "Again, it is clear that Dr. Lorincz in an eminent, highly accomplished doctor," compel a conclusion that both doctors are qualified to present the expert opinions contained in their respective Declarations. Accordingly, the Examiner must weigh the objective evidence provided by these two medical experts, not summarily dismiss such evidence as somehow being submitted by non-qualified individuals. Such dismissal is error.

In the Final Rejection of December 9, 2004, at page 7, the Examiner additionally took issue with the Declarations of Drs. Heuser and Lorincz by erroneously stating that Drs. Heuser and Lorincz relied on a number of publications to support their respective enablement opinions. Such publications were Strauer, Pagani et al., Hamano et al., Tse et al., and Perin et al. In fact,

the Declarants placed no such reliance upon these publications; and thus, there is no nexus between the Examiner's criticism and the respective Declarations. The Examiner's attention is directed to Paragraph 9 of the Declarations, Paragraph 8 of the Supplemental Declarations, and Paragraph 9 of the Second Supplemental Declarations, where it is indicated that the Declarants relied only upon Applicant's indicated disclosure and claims to reach the conclusion that one skilled in the medical art, armed with the relied upon information, would be able to practice the method set forth in the claims without need for resorting to undue experimentation. The publications mentioned by the Examiner form no part of the information relied upon by the Declarants. Thus, the Examiner's reading of the respective Declarations was erroneous.

The Examiner stated, at page 10 of the Final Rejection of December 9, 2004, "Therefore, the opinions of Drs. Heuser and Lorincz are not found to be persuasive, as it is based upon evidence that is found to be either irrelevant, not commensurate in scope with the claims, or relying on methods which were not disclosed in the specification as originally filed." The preceding paragraph demonstrates that the Declarants relied only upon Applicant's specification and claims; and thus the Examiner erroneously read the above-mentioned Declarations. The Examiner's sole criticism relating to the scope of the claims is that such scope is broader than that of the administration technique of Strauer. Clearly, Strauer's technique falls within the claims and may or may not constitute an improvement to the broader techniques disclosed in the specification. The scope of the claims is fully supported by the disclosure, and thus the Examiner's criticism has no merit.

Applicant submits that the Examiner's enablement determination is fatally flawed because the Declarations of Drs. Heuser and Lorincz were not accorded due weight. These Declarations were proffered as objective evidence in rebuttal of the Examiner's initial

determination that the claimed invention failed to comply with the written description and enablement requirements of the statute. Applicant believes that these experts' Declarations raise genuine issues of material fact regarding what the specification discloses to one skilled in the art. cf. In re Alton, supra.

It is well established that questions of whether a specification provides adequate written description and/or enablement of the claimed subject matter are issues of fact. The Declarations of Drs. Heuser and Lorincz raised genuine issues of material fact (evidence) regarding what the application disclosed to one skilled in the medical art, and the Examiner must weigh that evidence and render a decision based on the relative strength of Applicant's showing *vis-à-vis* her initial case for lack of enablement. The Examiner is charged with making sure that Applicant's objective evidence relied on guidance gleaned from the specification as filed and what was known to one skilled in the art and making sure that such evidence bears a reasonable correlation to the scope of the claimed invention.

The Examiner erred by dismissing the Declarations of Drs. Heuser and Lorincz without articulating a succinct explanation of how the Declarations failed to overcome her initial case for rejecting the claimed subject matter at issue. In re Oetiker, supra. The Examiner's dismissive conclusory statement that the Declarations were considered but not found to be persuasive does not rebut the thrust of Applicant's Declarations nor does it meet the spirit and letter of In re Oetiker, supra. It is well established that examiners, not being skilled persons in the art, must give weight to expert opinions rather than substitute their own opinion. See In re Neave, 370 F.2d 961, 152 USPQ 274, (CCPA 1967).

The standard for determining whether an applicant meets the enablement requirement of the statute was established in Mineral Separation v. Hyde, 242 US 261, 270 (1916). Although

§112 of the statute does not use the words "undue experimentation," the Courts have interpreted enablement to require the person skilled in the art to make and use the invention without resorting to more than routine experimentation, In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988). As recognized by the Court in Amgen, Inc. v. The Chugai Pharmaceutical Company, Ltd., 927 F.2d 1200, 18 USPQ 2d 1016 (Fed. Cir. 1991), the Wands factors are illustrative of, not mandatory to, finding a disclosure enabling. The present case illustrates the reason for that warning.

Although Applicant believes that the above arguments fully respond to the lack of enablement issue raised by the Examiner and should be dispositive of this issue, Applicant will hereinafter discuss the individual Wands factors for the sake of completeness.

It appears to Applicant that the basis for the Examiner's rejection for lack of enablement is stated on pages 19-20 of the Final Rejection of December 9, 2004, wherein the Examiner concluded:

> Due to the large quantity of experimentation necessary to determine how to administer cells intravenously or intraluminally to achieve repair of a distant dead or damaged heart portion, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of targeting cells to a distant site, and the breadth of the claims, it is determined that undue experimentation would have been required of the skilled artisan to practice the claimed methods.

It is again pointed out that claims 248 and 249 do not require heart repair, and accordingly, the Examiner's conclusion is erroneously based upon an unclaimed feature of the invention. In any event, for completeness, Applicant will treat the Wands factors below.

Except for determining and evaluating the impact of the level of skill of those in the art

regarding enablement, the above basis embodies the Wands factors. Obviously, the skill level in the art is important and necessarily impacts any analysis of the other Wands factors. In the Final Rejection of December 9, 2004, regarding claims 248 and 249, the Examiner failed to specifically discuss or weigh the Wands factor relating to skill in the art, either alone or in combination with other related factors. Applicant believes that the Examiner's failure to discuss, evaluate, and weigh the impact of the skill level upon each of the other enumerated Wands factors leads to an erroneous analysis. One must first identify the skill level in order to adequately evaluate the other inextricably intertwined Wands factors. Once the skill level is considered along with other evidence, Applicant believes that a conclusion of enablement is compelled.

As mentioned in MPEP Section 2164.01(a), the Examiner must weigh all evidence related to the Wands factors (emphasis added). The decision in In re Wands led to the grant of a patent, as the Court found that the PTO's determination of unpredictability was not supported by the evidence in the record. In reversing the PTO, the court specifically noted that the evidence in the record supported a finding of predictability. The Court further noted that the skill level in the art was high and that known materials were utilized in the practice of the invention in weighing the evidence. The instant fact situation is similar to that of In re Wands because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention. Applicant's evidence, in the form proffered by his experts, far outweighs any evidence regarding enablement supplied by the Examiner.

The Examiner's analysis of the Wands factor relating to the quantity of experimentation and amount of guidance required relies upon Strauer and Deb as evidence that large amounts of experimentation would be required to practice the claimed invention. As recognized by the

Court, such factors are illustrative of, not mandatory to, finding a disclosure enabling. See Amgen, supra. Applicant has already rebutted the Examiner's analysis of Strauer and Deb above, and such remarks need not be repeated. The Examiner's conclusion is at odds with the expert opinions of Drs. Heuser and Lorincz, which evince that one skilled in the medical art, armed with the knowledge of the disclosure, would be able to practice the method covered by the claims in issue without need for resorting to undue experimentation. The Examiner is merely basing such conclusion on unsound reasoning and mere opinion rather than upon material fact. Finally, considering that the skill level in the art is quite high, the amount of experimentation required to make and use the claimed invention would be *diminimus*.

Applicant believes that the Examiner has further mischaracterized Strauer, at page 16 of the Final Rejection of December 9, 2004, as evidence that, "a great quantity of experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result." In fact, no experimentation was involved in Strauer's feasibility trials; instead, Strauer achieved the expected result in the absence of experimentation. A careful reading of Strauer reveals that work performed during a Phase I trial was used as a basis for the article. As further stated in the article, Phase I trials do not involve a randomly allocated blind control group. Such Phase I work did not involve experimentation but was merely a feasibility trial utilizing autologous cells from the patients' bone marrow aspirate as a whole, rather than as a subpopulation.

A reasonable reading of Strauer indicates that the authors relied upon the prior work of others in determining cell population and cell transplantation factors; and thus, Strauer performed little, if any, experimentation in these areas. It is clear that the work performed by Strauer involved the selection of known materials and administration techniques rather than

conducting experiments designed to determine the effect of such materials and techniques. Hence, the Examiner's reliance upon Strauer as evidence that undue experimentation would be required is erroneous.

At page 16 of the Final Rejection of December 9, 2004, the Examiner stated the following:

> The evidence as a whole indicates that intravenous administration of cells to repair a dead or damaged portion of a heart has not yet been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and preventing them from re-migrating away from the site. As this problem has not yet been solved in the literature, and no suggestions for solving the problem are suggested in the specification as originally filed, a great quantity of experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result.

Such statement does not take into account that claims 248 and 249 do not require heart repair and, thus, is irrelevant to such claims. In any event, the Examiner's assertion is erroneous and is rebutted by Strauer, Wollert, and Deb, as discussed throughout this Amendment.

Applicant believes that the facts set forth above regarding Strauer do not support the Examiner's characterization of this evidence. Rather, Applicant believes that Strauer supports evidence of enablement of the claimed invention, not lack thereof. Like Applicant, Strauer used known administration techniques and known materials to achieve the new result of artery formation and heart repair. As demonstrated before, Deb did not attempt heart repair, and performed no experiments directed toward the claimed results. Accordingly, Deb has probative value only regarding confirmation that migration of cells to the heart occurs upon intravenous administration of cells and that new cardiac muscle is grown. Based on Strauer and Deb, Applicant believes that the Examiner has failed to establish that large amounts of

experimentation would be required to practice the claimed invention.

In regard to the amount of direction/guidance presented in the specification, Drs. Heuser and Lorincz have reviewed the specification and provided expert opinions based thereon that the invention defined in the claims is enabled by the specification. This is evidence that the specification provided sufficient direction and guidance to practice the invention of the claims in issue. The Examiner has failed to articulate wherein such disclosure relied upon by Declarants does not meet the necessary requirements for direction and guidance, and has not proffered any evidence to the contrary. Hence, the Examiner's comments amount to mere opinion, not evidence, and should be accorded no weight.

The next Wands factor addressed by the Examiner is the presence or absence of working examples. The Examiner generally concluded that the absence of working examples in the specification must be taken into account. Applicant does not disagree with such conclusion but believes that the presence of prophetic examples in the subject specification is entitled to probative weight when evaluating the totality of evidence. In this regard, the Examiner has failed to address the disclosure at page 46, lines 3-16. Such disclosure contains a prophetic example disclosing heart repair by seeding with cells immediately adjacent the dead cardiac muscle and growing new muscle and new arteries. Official Notice should be taken by the Examiner that "seeding" is a broad term, which includes intravenous or intraluminal injection, as well as other types of injection. One skilled in the art, reading page 46 in conjunction with page 45, would understand that "seeding" includes the intravenous and intraluminal modes found on page 45. Note further that Drs. Heuser and Lorincz based their opinions, in part, on such disclosure. Indeed, the MPEP Section 2164.02 specifically sanctions the use of prophetic examples as means for satisfying the enablement requirement of 35 U.S.C. §112, first paragraph.

Of course, a prophetic example, unlike work actually conducted or results actually achieved, describes an embodiment of the invention based on predicted results and serves to inform a person skilled in the art as to the working of the invention. It was error for the Examiner to deem that only working examples are relevant in the evaluation of this factor.

The next Wands factor addressed by the Examiner is the complexity of the invention. Applicant's disclosure is directed to skilled persons in the medical art, such as the Declarants. Obviously, subject matter that may appear complex and complicated to a non-skilled person is not complex and complicated to a person skilled in the medical art. It must be kept in mind that the present invention involves the administration of known materials using known administration techniques to achieve a new result, and complexity must be evaluated in view thereof. In other words, complexity may lie in the conception, but not in making and using the invention once the concept is understood.

The Examiner's reliance upon the Murry et al. publication (of record) (hereinafter "Murry") to establish complexity is misplaced. Murry is not concerned with the subject matter of the claims at issue in this portion of the rejection; i.e., intravenous and intraluminal administration of cells to a human heart. Rather, Murry simply administers cells by intramuscular injection to a mouse. This administration technique is notoriously old and well known in the art – certainly not complex. Thus, the Examiner's erroneous reliance upon Murry to establish complexity is necessarily flawed because the respective administration modes and patients of Murry and those in Applicant's claims 248 and 249 are distinct.

It is noted that the Examiner further alleged that Strauer is illustrative of complexity, apparently relying upon the fact that Strauer utilized a high-pressure intraluminal injection technique to administer cells. This aspect of Strauer has been discussed extensively above and

need not be repeated. In such prior discussion, Applicant mentions that Wollert successfully used an intraluminal infusion technique that did not require the use of Strauer's high-pressure technique. Such fact mitigates any inference of undue complexity in view of Strauer because Strauer's technique is not essential to the practice of the invention.

In the discussion of the Wands factor involving complexity, the Examiner considered that more than one embodiment may be required in cases that involve chemical reactions and physiological activity, citing Ex parte Hitzeman, 9 USPQ 2d 1821 (BPAI 1987); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); and Amgen Inc. v. Chugai Pharmaceutical co. Ltd., 927 F.2d 1200, 1212, 18 USPQ 2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991), and concluded that in the instant case no working embodiments were given. The Examiner's generalized reliance upon such case law, rather than upon any objective evidence relating to the claimed invention, is inapt because these cases address current law regarding predictability determinations, not complexity. In fact, in the Amgen case, there was evidence of unpredictability in the form of testimony by expert witnesses. These cases are not controlling in the present situation where evidence of predictability is present in the respective declarations. It is again emphasized that Drs. Heuser and Lorincz believe that the claimed results are predictable and that appropriate weight must be assigned to this evidence. In any event, Applicant's disclosure contains examples of various growth factors being utilized to form a new cardiac muscle and a new artery. Again, the Examiner appears to ignore or misinterpret relevant portions of the specification.

Certainly, Strauer, in any of the three publications, never states that intravenous administration of cells would be inoperative; in fact, Strauer 2003 (of record) in the section captioned, Route of Cell Administration, states that, "The intravenous route of administration is

easiest." Note further that intravenous administration is illustrated in the figure in such section. Based upon the above-mentioned disclosure, no skilled person in the medical arts would agree with the Examiner's conclusion, "Thus, Strauer specifically provides evidence of non-enablement of the instant claims reciting intravenous administration of cells." Clearly, the Examiner has misinterpreted Strauer's teachings. The Examiner's attention is also directed to the fact that other types of administration techniques are referred to as "preferred" in Strauer 2003. Obviously, a preference does not mean that other types of administration are not enabled.

In view of the above remarks, Applicant submits that making and using the claimed invention is not complex as alleged by the Examiner but rather is a straightforward procedure utilizing known materials and administration techniques. The Declarants' enablement opinions confirm such submission.

The next Wands factor addressed by the Examiner is the state of the art. It is noted that the Examiner has cited no art involving the treatment of patients with either intravenous or intraluminal techniques. The Examiner, at page 18 of the Final Rejection of December 9, 2004, characterizes the art as, "the majority of publications form [sic] this time were geared toward intramuscular administration rather than intravenous or intraluminal administration techniques." Actually, the only publication prior to Applicant's April 21, 1998 filing date is that of Murry. Murry is directed only to intramuscular administration, and no prior art was cited regarding intravenous and intraluminal techniques. This analysis misses the point because the Examiner omitted the fact that intraluminal and intravenous techniques were well established in the art for other purposes prior to Applicant's filing date. The Nabel et al. patent (of record) which was cited by the Examiner, is exemplary of such prior art. What was not established was that these

techniques could be utilized to administer growth factors, such as cells, to grow new cardiac muscle and new arteries and to repair a dead or damaged heart.

The next Wands factor addressed by the Examiner is "unpredictability." The Final Rejection of December 9, 2004, contains no objective evidence regarding this issue. The Examiner set forth no evidence and attempts to equate some unspecified "deficiencies of the evidence brought forth by Applicant" as evidence of unpredictability. Inasmuch as the Examiner failed to identify any such deficiencies, no probative weight can be accorded to support the Examiner's position. In contrast, Applicant has submitted strong, probative evidence in the Declarations of Drs. Heuser and Lorincz that the claimed invention is predictable.

The final Wands factor addressed by the Examiner is breadth of the claims. The Examiner observed, at page 18 of the Final Rejection of December 9, 2004, that, "although intravenous and intraluminal administration of certain drugs for certain effects may be routine, but intravenous and intraluminal administration of cells to repair dead or damaged heart tissue was not well-known in the art." Both aspects of this observation are correct. Once again, the Examiner has apparently failed to comprehend that Applicant has used old and routine administration techniques and old materials to achieve a new result, which is repair of dead or damaged heart tissue. This result constitutes Applicant's pioneering invention, which is deserving of broad protection.

Regarding the Examiner's contention in the Final Rejection of December 9, 2004, at the top of page 19, that, "Strauer et al. et al. [sic] and Deb et al. provide evidence that intravenous and intraluminal administration fail to deliver sufficient cells to the site of damage to achieve the required result," Applicant is at a loss to understand the relevance of such contention to the issue

of breadth of the claims. Such lack of understanding is compounded by the Examiner's further statement that, "However, all these details are off-point to the issue of the breadth of the claims."

The Examiner further stated at page 19 of the Final Rejection of December 9, 2004:

> The claims merely recite intravenous or intraluminal administration, and do not provide any other limitations (e.g., which veins, which lumens, how many cells, any other substances administered, etc.). Therefore the breadth of the claims is very large, a factor which is to be taken into account when making the determination of whether or not the amount of experimentation required by the skilled artisan to practice the claimed invention in its full scope is or is not undue.

Addressing the above limitations is well within the capability of one skilled in the medical art, as evidenced by the Declarations of Drs. Heuser and Lorincz. Like Dr. Strauer, both Dr. Heuser and Dr. Lorincz are well aware of intraluminal and intravenous techniques by virtue of their education and professional experience. Thus, there is no mystery why these experts concluded that the description contained in Applicant's specification regarding enablement is sufficient to practice the invention defined in claims 248 and 249. Obviously, a skilled physician, as contrasted to a layperson, would have little or no problem in using known administration techniques to inject known materials at an appropriate site in the body. One skilled in the art would have no difficulty in selecting dosages as discussed more fully below. The Supplemental Declarations of Drs. Heuser and Lorincz, at Paragraph 8, attest to this situation. It is submitted that the Examiner is bound to accept the expert opinions of Drs. Heuser and Lorincz and is not permitted to substitute her opinion for that of the experts. The Examiner cannot ignore such experts' opinions that predictable results would be obtained. See In re Alton, supra.

One final point remains. The Court in Wands reversed the PTO's lack of enablement

rejection concluding that the specification provided sufficient guidance and direction on how to carry out the claimed invention and presented examples. The Court also found that all the methods required for carrying out the invention were old and well known and that the level of skill in the requisite art was high. Applicant believes that this is "on fours" with the present factual situation where the level of skill was characterized by the Examiner as "admittedly high" and the claimed invention requires the use of old and well known materials and methods.

For the reasons stated above, Applicant submits that the Examiner's rejection of claims 248 and 249 for lack of enablement is erroneous and is not supported by the evidence discussed above. Accordingly, Applicant requests the Examiner to favorably reconsider and withdraw this rejection.

In addition to the above-discussed rejection of claims 248 and 249, the additional enablement rejection referred to on pages 22-26 of the Final Rejection of December 9, 2004, stated that:

> Claims 236, 238, 239, 243-253 and 256 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner further noted that, "The claims have been amended to recite growth of new cardiac muscle, and formation of a "new" artery." On page 25 of the Final Rejection of December 9, 2004, the Examiner states that the record does not support enablement for "the de novo growth of an artery as defined by Applicant" (emphasis added). In support of such conclusion, the Examiner apparently relied upon the factors set forth in Wands. However, unlike Wands, no specific weight was assigned to the skill in the art by the Examiner. Moreover, the

Examiner provided only argument and failed to cite specific objective evidence supporting such conclusion. Further, the Examiner failed to consider Applicant's objective evidence regarding enablement that was proffered in the Declarations of Drs. Heuser and Lorincz. The Examiner's failure to consider such material evidence is erroneous and leads to the flawed conclusions set forth in the Final Rejection of December 9, 2004.

Applicant believes, based upon the Examiner's remarks in the Final Rejection of December 9, 2004, that this rejection is predicated upon an erroneous reading of the subject matter of the claims. First, only claims 238 and 239 require repair of a dead/damaged portion of a heart. However, the Examiner appears to have treated all claims as though repair is required. This is error and leads to an incomplete treatment of the other claims. Second, it is evident that, as in the case of the co-pending appeal of Applicant's patent application, Serial No. 09/794,456, the Examiner has attempted to interpret the term "new artery" as being limited to *"de novo* arteries." No such limitation exits in the language of the claims or in the specification; and, accordingly, it is error to condition this rejection upon such non-existent language. The Examiner has misconstrued and misinterpreted the subject matter of the claims rather than treating the actual claimed subject matter. Thus, this rejection conditioned upon *'de novo* arteries" must fail because the Examiner's claim interpretation is erroneous.

As pointed out above, Applicant believes that an identification of the skill level in the art is a critical factor because such level obviously impacts any meaningful analysis of the other Wands factors.

At the last line of page 25 of the Final Rejection of December 9, 2004, the Examiner stated that "the level of skill in the art is admittedly high." The level of skill is further amplified by the Examiner's recognition on page 25, lines 4-6 of the Final Rejection of December 9, 2004,

that medical professionals who practice in the field of the claimed invention, "must endure years of study and training before being certified to attempt such procedures on human patients." Drs. Heuser's and Lorincz's education, training, and experience, clearly meet such high skill level, which further exacerbates the Examiner's erroneous failure to consider and weigh Applicant's declaration evidence with regard to the claimed invention's enablement.

Regarding the Wands factor involving quantity of experimentation required, the Examiner alleged, in the Final Rejection of December 9, 2004, that a very large amount of experimentation would be required to make and use the claimed invention. Specifically, the Examiner pointed to pages 1916-1918 of Strauer as evidence that critical experimentation is required to determine "what cell populations to use, what delivery method to use, and when cells should be transplanted." Applicant submits that at the time of the invention the relevant knowledge was such that one skilled in the medical art would readily recognize and determine how to select cell population, delivery means, and cell transplantation timing following a heart attack. A critical reading of Strauer clearly evinces that little or no experimentation was performed or reported.

Such recognition and determination fall within the skill of the medical art and require no more than routine experimentation, as confirmed by the expert opinions in the Declarations of Drs. Heuser and Lorincz. Applicant submits that the Examiner has exaggerated the amount of experimentation required. Strauer did not report that a large amount of experimentation was conducted. To the contrary, Strauer selected a cell population that worked and did not report any cell populations that did not work. There is no evidence that these skilled medical practitioners required a large amount of experimentation, if any, in this regard. The Examiner's attention is further directed to the goals of Strauer regarding delivery means and the timing of cell

transplantation. Strauer desired to select the "most efficient' application method and to select an "ideal" time point for delivery. In regard to timing of treatment, it is clear that this factor is not critical because Strauer initially reported a treatment eight weeks following a myocardial infarction. In a subsequent 2005 publication (of record), Strauer reported successful treatment of patients who had experienced myocardial infarction up to eight years earlier. Thus, the Examiner's reliance upon timing of treatment as evidence of undue experimentation is without merit because Strauer demonstrated that a wide range of treatment times are appropriate. Strauer's determination of the "most efficient" and "ideal" factors clearly does not rise to evidence of a large amount of experimentation.

The Examiner also stated at page 23 of the Final Rejection of December 9, 2004, that, "despite all of this work, growth of new cardiac muscle was not achieved." While it is not clear what the Examiner meant by "this work," it is clear from page 1913 of Strauer that transplantation of autologous BMC's improved cardiac function significantly and such, "marked therapeutic effect may be attributed to BMC-associated myocardial regeneration and neovascularization." Strauer's results are confirmed by Wollert, where new cardiac muscle and new arteries were grown in a human heart by BMC-associated transplantation. Wollert conducted a 60 patient randomized-controlled trial, which is universally recognized as the "gold standard" for clinical trials. In addition, Wollert utilized full color cardiac MRI images to document the improved functional recovery achieved in the BMC group of patients. The Deb study, which involved sex mismatched bone marrow transplants, incontrovertibly confirmed through autopsy proof that BMC's form new cardiac muscle in human hearts. The Examiner, at page 14, lines 15 and 16, admits that cardiomyocytes were formed by Deb. This admission is at odds with the Examiner's allegation. In any event, Deb performed no experimentation regarding

how to achieve the claimed results.

Applicant points out that the Second Supplemental Declarations of Drs. Heuser and Lorincz, at paragraph 9, contain the opinion that one skilled in the medical arts, having read paragraphs 6-8 of the Second Supplemental Declaration, would be enabled to practice the claimed method and predictably anticipate the results defined therein without need for resorting to undue experimentation. The Examiner failed to address this strong, compelling evidence from highly skilled medical practitioners affirming enablement. Accordingly, there can be no question that no more than routine experimentation would be required to make and use the claimed invention.

Regarding the Wands factor of direction/guidance, in the Final Rejection of December 9, 2004, the Examiner alleged that the specification provides, "no guidance along the lines of the details worked out by Strauer et al." The appropriate test for enablement relates to the disclosed invention of Applicant, not Strauer. The fact that both Drs. Heuser and Lorincz find the details contained in the instant specification to be enabling should be dispositive of this matter. There is no requirement that an applicant must anticipate the nature of future experimental work and then provide experimental details thereof in order to satisfy the enablement requirement. This is especially true when the future work is designed to improve or optimize the applicant's invention. All that is required is that an applicant provides sufficient detail to enable a skilled person in the art to make and use the claimed invention. Applicant's specification has provided such detail by 1) describing in broad terms the method and manner for practicing the invention, 2) providing specific examples in the way of detail, and 3) supplying prophetic examples detailing how to practice the claimed invention to achieve the claimed results.

In the Final Rejection of December 9, 2004, the Examiner gratuitously cited and partially

discussed a variety of non-elected inventions in the topic of guidance. Applicant is uncertain why the Examiner wishes to potentially cast a cloud on such non-elected inventions by offering a premature and irrelevant "opinion" regarding such inventions. Applicant believes that such "opinions" are improper, inaccurate, do not appear to have been well researched, are potentially prejudicial to Applicant, and are obviously irrelevant to the claimed invention.

As noted in the preceding paragraph, the Examiner has improperly focused upon several non-elected inventions. It is noted that the Examiner imposed a 94-way restriction requirement at the outset of prosecution. It appears to Applicant that the Examiner utilized an extremely narrow focus in determining that 94 separate and independent inventions were present in the claims of the instant application. As a result of such narrow focus, Applicant, a small entity, does not have the resources necessary to file and prosecute all of the remaining 93 inventions and thus likely will not obtain potentially valuable patent assets. The Examiner's attempt at this time to "examine" the above-mentioned non-elected inventions, despite making the restriction requirement, is unwarranted and amounts to inconsistent and potentially prejudicial prosecution.

The Examiner, relying on Genentech Inc. v. Novo Nordisk A/S, (CAFC) 42 USPQ 2d 1001 (1997), asserted that, "The courts have also stated that "[t]ossing out the mere germ of an idea does not constitute an enabling disclosure...[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Applicant has demonstrated above that the specification provides ample guidance to enable one skilled in the art to carry out and practice the claimed invention. Certainly, Drs. Heuser and Lorincz had no difficulty in reading and understanding the guidance set forth in the specification regarding making and using the claimed invention.

Regarding the Wands factor involving working examples, in the Final Rejection of December 9, 2004, the Examiner concluded that there are no working or prophetic examples directed to the elected invention. In support of such conclusion, the Examiner considered that even though prophetic examples were present, none of such examples are, "directed to administration of cells to grow cardiac muscle or a new artery." The Examiner appears to have overlooked Applicant's disclosure at page 46, lines 3-16, which contains a prophetic example of heart repair using cells to grow new muscle and new arteries wherein cells are seeded, "[I]mmediately adjacent to dead cardiac muscle." Note further that Dr. Heuser and Dr. Lorincz based their opinions, in part, on such disclosure. It was error for the Examiner not to assess the evidentiary weight of such disclosure.

It is well established that examples, whether working or prophetic in nature, are not required in an application. In the present case, the absence of a working example is of little consequence because the two Declarants have opined that the specification is enabling.

Regarding the Wands factor involving complexity, the Examiner alleged, in the Final Rejection of December 9, 2004, at page 25, that the invention is highly complex and pointed to all of the publications of record, especially Strauer, to support such allegation. The reason that Strauer does not support the Examiner's position has already been extensively discussed above in connection with the prior enablement rejection for claims 248 and 249. The "other publications of record" are not identified or specifically addressed by the Examiner.

The Examiner further supports such allegation with a generalized statement that, "All inventions involving administration of active agents of any kind to a patient to achieve a physiological reaction are complex." Applicant submits that complexity must be considered in light of the context of the instant invention, rather than in a general sense. Applicant points out:

1) that all disclosed administration techniques were known in the art prior to the effective filing date of the application; and 2) that cells, including stem cells, along with associated preparation and handling techniques, were known in the art prior to the effective filing date of the application. What was not known or conceived by another was that, if cells were administered in accordance with the invention, new cardiac muscle and new arteries would be grown in a heart. This is Dr. Elia's novel and unobvious contribution to the medical art. The invention, once understood by one skilled in the art, is straightforward to practice, not complex, as alleged by the Examiner.

Applicant recognizes that heart repair is a complex art; however, the skill level of the person working in this area is comparably high. For example, a skilled person in the medical art, such as Dr. Heuser, upon reading applicable portions of Applicant's specification, would be able to practice the claimed method set forth without need for resorting to undue experimentation. In this regard, see the Second Supplement Declaration of Dr. Heuser. What may appear to be complicated to a layperson certainly would not be complicated to such highly trained and skilled persons.

Regarding the Wands factor involving state of the art, the Examiner, in the Final Rejection of December 9, 2004, at page 25, cited two technical publications; namely, Balsam et al., 2004 Nature 428:668-673 and Ziegelhoeffer et al., 2004, Circulation Research 94:230-238, both of which bear a 2004 publication date. The Examiner asserted that the publications were probative evidence of the state of the art. Reliance upon such citations is misplaced because, as best understood by Applicant, the state of the art regarding enablement is that at the time of the filing of the instant application.

By citing the two above-mentioned publications, the Examiner appears to be alleging that such publications are contradictory in that different theories relating to mechanisms for cardiomyocyte and artery formation have been reported by workers in the art. The correctness of any theory of artery formation advanced by these references is irrelevant to Applicant's disclosed and claimed invention. Whether new arteries are formed because of angiogenic factors released by the cells, by differentiation, or by another mechanism, is important from a scientific viewpoint but is not critical to Applicant's claimed method of stem cell implantation for growing new cardiac muscle and new arteries. The claims in issue neither recite nor require a particular theory of operation. It is axiomatic that an applicant is not required to disclose or claim a particular theory of invention in order to comply with the first paragraph of the statute. Both Balsam and Ziegelhoeffer conducted tests on murine models, not on a human patient. Accordingly, such tests are deemed to be less relevant to the Examiner's new issue than those conducted on human patients by the Strauer, Wollert, and Perin publications and in Perin's July 18, 2005 report entitled, "Transendocardial Autologous Bone Marrow Mononuclear Cell Injection in Ischemic Heart Failure" in the publication Circulation (attached hereto as Exhibit N and hereinafter referred to as "Perin 2005"). The Examiner further alleges that Balsam is evidence that BMC's, "do not in fact, contribute to myocardial regeneration (i.e., growth of cardiac muscle)." The difference between Balsam's study and previous work is the nature of BMC's used. Balsam obtained whole bone marrow harvested from mice and then isolated several purified and highly purified subsets of cells, which is distinct from the whole bone marrow used by the other workers. Orlic, Strauer, Deb, Perin, and others have repeatedly and independently reported BMC's can and do form new cardiomyocytes. Thus, the Examiner's attempted comparison based upon these publications is clearly invalid because different cellular

materials were used in the respective publications. Balsam does not, in fact, support that the art is contradictory, and it is insufficient to establish a contradictory state of the art. Moreover, the autopsy proof of new cardiomyocyte formation in humans offered by Deb and Perin 2005 satisfies the "best evidence" rule in regard to this issue.

Additionally, the Examiner in the Final Rejection of December 9, 2004, at page 25 stated that, "None of the numerous post-filing date publications put on record by Applicant to support enablement of the claimed invention report the *de novo* growth of an artery as defined by Applicant, including Strauer et al." The above quoted passage contains three errors. First of all, Applicant did not rely upon any publications, including Strauer, to support enablement of the claimed invention but instead relied on Strauer as confirming operability. Regarding the claimed invention's enablement, Applicant relies upon the instant specification as well as the objective declaration evidence of Drs. Heuser and Lorincz. Even a cursory reading of the respective Declarations indicates that both Declarants relied solely upon identified portions of the specification and the current claims to conclude that enablement was present. Secondly, Strauer, Wollert, and Perin 2005 confirm that new cardiac muscle and new arteries are grown in a human heart. Thus, the Examiner's statement is obviously erroneous. Moreover, Strauer, Wollert, and Perin provide rebuttal evidence that heart repair (specified in claims 238 and 239) does, in fact, occur by practice of the claimed invention. Thirdly, no publications were relied on to show *de novo* growth of an artery. This is not surprising because such *de novo* artery terminology is not present in Applicant's claims or specification and appears to be the Examiner's creation. The Examiner apparently mentioned Strauer in this regard. However, Strauer reports, at page 1913, the achievement of "neovascularization" but nowhere uses the term *de novo* artery. More recently, Perin 2005, in the autopsy report, characterized the formation of arteries as "new" and

did not use the term *de novo*. Thus, Applicant remains confused as to the rejection regarding the meaning of *de novo*, which term does not appear in the claims.

By apparently predicating this enablement rejection upon whether the claims are limited to the formation of *de novo* arteries, the Examiner has again taken a position that is inconsistent with her examination during the prosecution of the Weiss patent application. The Examiner's attention is once more directed to the Weiss patent file history, which indicates that no enablement issue was raised regarding whether the term "new", as used by Weiss at column 12, lines 48-51 in connection with the *in vivo* formation of new dopamine neurons, was limited to *de novo* formation of such neurons. Like Applicant's application, the term *de novo* does not appear in the Weiss patent. Applicant's perusal of the Weiss patent indicates that any such rejection would have been unwarranted because it is clear from the balance of the Weiss patent specification that dopamine neurons were formed by the process of the invention and that "new" adequately describes such formed neurons. Likewise, Applicant has used the term "new" to describe the results of his invention, i.e., new cardiac muscle and new arteries, and has presented adequate description in the specification for those skilled in the art to understand the meaning of the term. Applicant submits that the above-mentioned fact situation indicates that the Examiner applied an erroneous and inconsistent examination standard to the instant application and that as a result, Applicant has been denied procedural due process.

By way of background, the term "new" was added to the claims following comments made by the Examiner's supervisor, Dr. Yvonne Eyler, during the January 6, 2004 interview to distinguish Applicant's heart repair method from the fused tissue obtained by Murry. Following such comments, Applicant's counsel stated that the claims would be amended to include the words "forming (or growing) new arteries" rather than "forming (or growing) arteries" and

further pointed out that the specification supported such amendment. Applicant stated that such amendment would be made to more clearly define differences over Murry. As a result of the interview, Applicant believed that the three Examiners attending the interview, including Examiner Kemmerer, understood the meaning of the word "new" in the context of the invention. Obviously, Applicant was surprised when Examiner Kemmerer raised the *de novo* artery issue.

Applicant believes that the word "new" speaks for itself when viewed in context of Applicant's specification and claims. As pointed out in the specification, Applicant forms new arteries and new cardiac muscle as a result of the inventive method. The Examiner is attempting to obscure the clear meaning of an ordinary word by suggesting that the artery "must be formed *de novo* and not merely repair, growth, or re-direction of an existing artery." The word "new" in the context of the invention simply means an artery that is newly formed or grown by Applicant's process. See the specification at page 44, line 19 to page 46, line 16; Example 19 at page 55, line 13 to page 57, line 3; and Example 36 at page 62, lines 1-10, as read with Example 18. In other words, the formed artery, following completion of the growth process, was not present in such form prior to conducting such process. Obviously, new tissue growth or formation is involved. The meaning of the phrase "growing a new artery" is thusly set forth above, despite the Examiner's highly improper attempt to redefine the word and then construe the claims to be limited to the Examiner's definition. It is the Examiner, not Applicant, that is implying that the newly formed artery must involve "*de novo* growth of an artery." Such implication is clearly improper because it is incumbent upon an applicant, not an examiner, to provide terminology defining an invention. What was accomplished by the amendment was to make explicit what was implicit, i.e.; that a new artery was formed.

It is also pointed out that neither Dr. Heuser nor Dr. Lorincz had any difficulty understanding the claim limitation "growing a new artery" because both experts reached the conclusion that the disclosure enabled the subject matter of the claims. Thus, Applicant believes that the Examiner likewise should not have any difficulty understanding that the claims simply mean growing a new artery and that such growth is well understood by a skilled person in the medical art.

The claims are not limited to *de novo* artery formation because Applicant's specification and claims used the language "new" in describing the claimed invention. Moreover, the Examiner has not adequately defined the meaning of the term *de novo* as it relates to the formation of arteries nor has the Examiner proffered any evidence of the prior art's use of such term in regard to the formation of new arteries at the time of Applicant's invention. Under these circumstances, the Examiner's attempt to redefine and delimit the claimed invention is improper.

Applicant was not familiar with the terminology *de novo* arteries at the time the application was filed. Obviously, an applicant cannot be expected to be clairvoyant and use unfamiliar, later-developed terminology in describing and claiming an invention. It is error for the Examiner to create terminology defining Applicant's claimed invention; deem that the claims are, somehow, limited to such undefined terminology; and then make a rejection based upon such terminology and claim interpretation.

The claims, for reasons described above, are not limited to *de novo* formation of new arteries.

In summary, it is evident to Applicant that the Examiner improperly characterized the state of the art by relying upon the Balsam and Ziegelhoeffer publications, as well as fabricating

an issue involving *de novo* arteries. Accordingly, the Examiner has presented no meaningful evidence in evaluating the state of the art that would support a finding of lack of enablement.

Regarding the Wands factor involving predictability, the Examiner alleged at page 26 of the Final Rejection of December 9, 2004, that, "administering active agents to a living patient to achieve a physiological response" is unpredictable, citing Ex parte Hitzeman, 9 USPQ 2d 1821 (BPAI 1987); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical co. Ltd., 927 F.2d 1200, 1212, 18 USPQ 2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Such cases are inapposite because in those cases, unlike in the present case, no evidence regarding predictability was present. In any event, no nexus was provided by the Examiner to establish that such legal tenant would be applicable to the facts of the instant application.

Regarding the Wands factor involving the breadth of the claims, Applicant believes that the breadth is commensurate in scope with the pioneering nature of the invention. The Examiner has presented no prior art that causes Applicant to limit his claims further than those currently under examination; and therefore, Applicant is entitled to such breadth. In the Final Rejection of December 9, 2004, the Examiner, at page 26, stated that, "The elected invention is directed to a method of administering any type of cell to an undefined area of the body of a human patient to grow new cardiac muscle and a new artery (of any type or location)." Regarding the first point, page 45, lines 1-4 of the specification broadly describes administering, "a gene or other genetic material into muscle at a desired site." More specifically, directions are given to those skilled in the art for selecting a desired site and include such factors as, "size, vascularity, simplicity of access, ease of exploitation, and any other desired factors." Page 46, lines 3-10 of the specification describes seeding immediately adjacent to dead cardiac muscle with appropriate

cells, genes, or other genetic material. In addition, page 45, lines 19-21 describes injecting a genetic material (in this case, a gene) into cardiac muscle to form cardiac muscle and artery to revive or replace a dead portion of the heart. Example 18 is directed to injecting growth factor into cardiac muscle immediately adjacent a clogged artery, and Example 36 is directed to injecting growth factor into two sites in the coronary artery adjacent damaged areas. Such identified disclosure is commensurate in scope with the scope of protection sought for the claims and, obviously, is limited by the claimed results.

Applicant notes that the Examiner raised the issue of dosages in the summary of the Final Rejection of December 9, 2004, at page 26, lines 15-19, and connected such issue with the breadth of claims Wands factor. Examples 19 and 36 specifically describe dosages for intramuscular injection.

It would be a routine matter to apply proper dosages, via either intravenous or intraluminal administration, for at least several reasons.

Firstly, "... it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. ...." MPEP Section 2164.01 (c).

Secondly, during the examination of the Weiss patent, the Examiner never raised the issue of dosages, either in the rejection or in the analysis of the Wands factors. Like the instant application, the Weiss patent did not describe a dosage range but rather described dosages at column 6, lines 19-27 as:

> An "effective amount" is an amount of a therapeutic agent sufficient to achieve the intended purpose. The effective amount of a given therapeutic agent will vary with factors such as the nature of the agent, the route of administration, the size and species of the animal to receive the therapeutic agent, and the purpose of the administration. The effective

> amount in each individual case may be determined empirically by a skilled artisan according to established methods in the art.

Both the Weiss patent and the instant application disclose specific dosages in their specifications, and their respective claims do not contain dosage limitations. However, unlike in the Weiss prosecution, in the instant prosecution, the Examiner adopted and applied a different enablement standard regarding dosages. Such inconsistent examination is improper because all applicants are entitled to the same administrative due process.

Thirdly, Applicant's specification describes new artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25×10^6 (Example 36) to approximately 12.5×10^6 (Example 19). Available off-the-shelf cDNA clones (nucleic acids) are directly injected into either the cardiac muscle (Example 19) or the coronary artery (Example 36). Each example describes forming a new artery and repairing a damaged heart with increased coronary blood flow. Each example also discloses slowly injecting the growth factor to avoid any carry away. While these examples employ nucleic acids, one skilled in the art reading the specification, which teaches that cells, i.e., stem cells (BMC's) possess equivalent activity to genes (nucleic acids) and other genetic material, in forming a new artery and repairing a dead or damaged portion of a heart, would be able to easily extrapolate the number on a weight basis of mononuclear cells required to obtain equivalent results. Note in this regard that Strauer discloses injecting six (6) to seven (7) times with 1.5 to 4×10^6 cells without disclosing any difference in results over the entire dosage range. Therefore, there is no significant clinical difference between Applicant's 6.25 to 12.5×10^6 and Strauer's 9 to 28×10^6 dosage ranges. Further, such skilled person would understand that intravenous or intraluminal administration routes would generally require larger doses than the direct injection route of Examples 19 and 36, and, for

example, simply doubling the dosage to 12.5 to 25 x 10^6 cells would essentially encompass Strauer's entire range. It is clear from Strauer that there is no risk for over-dosing, particularly using autologous BMC's, which are contemplated in Applicant's specification.[1] cf. In re Bundy, 642 F. 2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981).

Fourthly, both Drs. Heuser and Lorincz have stated, in paragraph 8 of their respective Supplemental Declarations, that dosages are a matter of routine medical practice and then have enumerated various factors that skilled physicians routinely consider in this regard. Such Declarations raise a genuine issue of material fact that cannot be ignored by the Examiner in the analysis of this Wands factor.

The evidence proffered by Applicant in the above four paragraphs makes it clear that undue experimentation is not required to select an appropriate dosage in the practice of the claimed invention.

It is again pointed out that the Examiner, in the Final Rejection of December 9, 2004, made no comment on the record regarding the merits of the Second Supplemental Declarations of Drs. Heuser and Lorincz, which confirmed enablement of the claimed invention. The Examiner's failure to consider and evaluate the evidentiary value of the two expert opinions amounts to error for reasons already set forth in earlier portions of this Amendment. See In re Alton, supra. If the Examiner takes issue with such Second Supplemental Declarations, it is incumbent upon her to explain her position. Drs. Heuser and Lorincz rendered opinions that the formation of new cardiac muscle and new arteries was enabled. It was further error for the

[1] The conversion for dosages of nucleic acids to corresponding dosages of cells was conducted as follows. Examples 19 and 36 specified dosages of 500 micrograms (ug) and 250 ug, respectively. The weight of nucleic acids of an average cell was considered to equal 40 picograms (pg). The described dosages of 250 and 500 ug when converted to pg by multiplying by 10^6 equals 250 x 10^6 pg and 500 x 10^6 pg. Since nucleic acids of an average cell have an average weight of 40 pg, a conversion is made by dividing 250 x 10^6 and 500 x 10^6 by 40 to arrive at the equivalent cell dosages, which are 6.25 x 10^6 and 12.5 x10^6, respectively.

Examiner not to have weighed the probative value of such expert opinions during her analysis of the Wands factors.

As mentioned above, the Court in Wands reversed the PTO's lack of enablement rejection concluding that the specification provided sufficient guidance and direction on how to carry out the claimed invention and presented examples. The Court also found that all the methods required for carrying out the invention were old and well known and that the level of skill in the requisite art was high. Applicant believes that this is "on fours" with the present factual situation where the level of skill is admittedly high and the claimed invention requires the use of old materials and old methods. Applicant believes that the results described in prophetic Examples 19 and 36 discussed earlier were confirmed by the work of Strauer, which used equivalent dosages of BMC's for heart repair and thus elevates the level of these prophetic examples to that of working examples. MPEP Section 2164.06.

The Examiner summarized this rejection at page 26 of the Final Rejection of December 9, 2004. Such summary paraphrases all the Wands factors, except for the factor involving a determination of the skill level in the art. Clearly, the skill level in the art impacts the evaluation of all of the Wands factors and should have been considered by the Examiner in this context. The Examiner's failure to consider the skill level factor, in combination with the other factors, results in a flawed analysis. It is again noted that the Examiner's discussion regarding state of the art appears to have been predicated upon a lack of enablement for achieving *de novo* formation of an artery. Such aspect of the rejection is erroneous because the claims do not recite nor are they limited to the term *de novo* artery.

Applicant believes that the Examiner has failed to articulate adequate support for the rejection. Even assuming, *arguendo,* that the Examiner has somehow made out an initial *prima*

facie case of lack of enablement, In re Oetiker, supra., the Examiner has failed to adequately explain how the Declarations of Drs. Heuser and Lorincz failed to overcome such a *prima facie* case. "A declaration ... is, itself evidence that must be considered." See MPEP Section 2164.05. Applicant believes that these Declarations are sufficient to shift the burden of going forward with evidence back to the Examiner. It was error for the Examiner to determine patentability without considering the entire body of evidence in the record. In re Oetiker, at 1445, 24 USPQ 2d at 1444. Accordingly, Applicant requests the Examiner to favorably reconsider the rejection of claims 236, 238, 239, 243-253, and 257-269.

In the February 16, 2006 Office Action, the Examiner raised several new issues regarding enablement.

The Examiner criticized Applicant for not pointing out any specific sections of the specification that describes specific materials and administration routes. Such sections of the specification have been extensively pointed out in this record. The Examiner is again reminded that Applicant has disclosed a generic invention involving the administration of growth factors, including cells, to achieve the novel results of the invention. In this regard, the Examiner's attention is directed to the portions of the specification cited in the Summary of the Invention section of Applicant's previously filed Appeal Brief. For the Examiner's convenience, such section is reproduced as Exhibit O attached hereto. In addition thereto, the record is replete with references to portions of the specification that support the claimed invention. The Examiner is also referred to the portions of the specification relied upon by Drs. Heuser and Lorincz in rendering their respective opinions.

At pages 7 and 8 of the February 16, 2006 Office Action, the Examiner appears to be confused as to the state of the art that existed as of Applicant's filing date. As best known to

Applicant, and reflected by the instant record, the administration techniques and growth factors set forth in the specification were individually known prior to Applicant's filing date. The Nabel et al. patent (of record) cited by the Examiner is evidence of the prior art's use of balloon catheter for precisely placing cells in a damaged area including at the site of a myocardial infarction. The Examiner on page 12 of the November 28, 2003 rejection admitted that, "Using an angioplasty balloon to administer the cells...was well known in the art at the time of the invention." Those skilled in the art would recognize that Nabel et al's administration technique could be used in practicing the invention for placing growth factors (genetic material, including cells) with an angioplasty balloon as described in words on page 45 of the subject application. What was not known, however, was the inventive concept that such administration techniques and materials could be combined to produce the novel and unobvious results of the invention.

The Examiner, at page 8 of the February 16, 2006 Office Action, appears to be alleging that Applicant has improperly picked and chosen among unconnected sections of the specification in an "attempt to capture another research group's post-filing discoveries." Such allegation appears to have been made without any evidentiary support or understanding of the imputation thereof and hence is unwarranted, troublesome, and outside the "pale." Applicant and counsel are understandably perplexed by such statement. If the Examiner is attempting to insinuate that Applicant is a "bad actor" and trying to "game" the patent system, this insinuation should be clearly made of record and supported. Indeed, the factual situation is to the contrary. Applicant described and claimed the invention set forth in Groups 79 and III prior to any knowledge of any other research group's activities that are relevant to the elected claims. Such elected claims fall within the narrow scope accorded by the Examiner during the restriction requirements, and subsequently added claims also fall within such scope. Hence, the Examiner's

allegation is clearly without merit. A full and detailed explanation, bottomed on fact, supporting the Examiner's allegation is requested in the event that such allegation is not expressly withdrawn from the record.

Also at page 8 of the February 16, 2006 Office Action, the Examiner considered that Perin teaches "intramuscularly forms of administration" and thusly "cannot be used to support enablement of the rejected claims which recite intravenous or intraluminal administration of cells." Such statement, however, appears to admit that other types of administration, including Perin's intramuscular and Nabel et al.'s angioplasty balloon, are enabled and within the scope of the disclosed invention. What the Examiner does not seem to understand is that while Perin serves to confirm or verify the working of Applicant's invention, enablement springs from Applicant's specification, not from post-filing date publications, such as Perin.

While it is not clear from the aforesaid Office Action that the Examiner duly considered Perin 2005, this publication provides autopsy confirmation of the growth of new blood vessels and new muscle in the heart of a human patient following intramuscular administration of bone marrow stem cells. This publication also conforms with the description, at page 46, lines 3-7, of Applicant's specification calling for implanting cells to promote the growth of new muscle and new arteries in a human heart.

Applicant respectfully believes that the application is in condition for allowance; and a notice to such effect is requested. However, should the Examiner decide to not withdraw any of the rejections of record, the Examiner is requested to present a clear, non-ambiguous basis for all remaining rejections that reiterates and specifically identifies all portions of the record being relied upon. The Examiner is also requested to fully treat and rebut all of Applicant's arguments and associated evidence. Such treatment obviously includes an identity and weighing of the evidence

submitted by Applicant with that proffered by the Examiner, including Applicant's rebuttal remarks and accompanying evidence. Following the requested action would then define any remaining issues and serve to place the case in condition suitable for further review. Applicant is simply requesting that the Examiner follow the tenants of compact prosecution and the Final Rejection Practice (Statement of Grounds) outlined in MPEP Section 706.07. Otherwise, Applicant will be denied administrative due process.

Should the Examiner have any questions or wish to discuss any issues, a phone call to Applicant's attorney would be appreciated.

Respectfully submitted,

Dated: 06/22/06

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